Response to Draft Sulfuryl Fluoride

Risk Characterization Document

(California Department of Pesticide Regulation dated March 16, 2004)

by

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EXECUTIVE SUMMARY

Risk managers must rely on the Risk Characterization Document (RCD) to make decisions about the regulatory disposition of sulfuryl fluoride (SF), which is currently marketed as Vikane™ gas fumigant. It is imperative that the RCD present the toxicology and exposure information in both a scientifically credible and understandable manner. Because risk assessment involves interpretation of data, it is important that the path from data to interpretation and the scientific basis underlying the interpretations be transparent. Dow AgroSciences' review of the Vikane final draft RCD revealed a number of incongruities that obscure the correct interpretation of the toxicology database for SF and the appropriate application of these data for purposes of quantitative exposure and risk analysis. The areas that had the most significant impact were misinterpretation or misunderstanding of the acute neurotoxicology study design and mismatching toxicology study duration with human SF exposure duration. These particular areas are critical because the appropriate interpretation of the toxicology data reveals that MOEs exceed 100 when appropriate durations and associated exposure scenarios are relied upon. The most important errors are summarized as follows:

1) Characterization of 10x "maximal" use rate at 10 times the initial concentration is incorrect. Information is provided to clarify that the 10x target is achieved by a combination of increased dose x increased holding time.
2) Acute residential exposure was overestimated by 25% to several-fold depending on the scenario due to elimination of pertinent data and unsupported assumptions about reentry time relative to clearance. The rat absorbed dose for the acute toxicity NOAEL concentration was underestimated by 22% in the RCD due to inappropriate interpretation of study duration. Resulting acute MOEs were significantly underestimated.
3) Potential short term exposure was greatly overestimated because it was averaged over 7 days and not the 14-day duration of the toxicology study. The net result was a significant underestimation of short-term MOE.
4) There is no subchronic (90 day) duration exposure to residents or bystanders, although it was calculated. This is because Vikane fumigation is a relatively rare event in neighborhoods, and the duration of exposure can be measured in hours not days, weeks, or months.
5) Chronic exposures were estimated for residents and bystanders assuming annual fumigation of their homes, a situation that does not occur. Also, handlers were assumed to work 52 weeks of every year for 40 years. The net effect was a gross underestimation of chronic MOE.
6) The short-term and intermediate-term exposures were not amortized to reflect actual frequency of use by workers resulting in underestimation of margins of exposure by approximately 2-fold.
7) The chronic toxicity endpoint was, in fact, derived from a subchronic-duration rat reproductive toxicity study despite the existence of an acceptable chronic study. The rat exposure regimen in the

reproductive toxicity study was 7 days per week for 70% of the duration, unlike the design of all the other intermediate to long-term studies. Had the chronic toxicity NOAEL been derived from the CDPR-accepted chronic study for a true adverse effect, it would be 4-fold greater.

8) The range of the refined MOEs (450 to 70,890 for workers and 106 to 7,087 for residential subpopulations) using realistically conservative exposure assumptions and appropriate interpretations of the SF toxicological data all satisfy the minimum regulatory target of 100. The MOEs calculated and described within this document support the perspective of Vikane uses in the State of California as representing acceptable human inhalation exposure and risk potential when handled in conformance with product label directions and state regulations.

There are additional technical and policy issues in the RCD that are discussed in this document. Each of these issues has significant bearing on the regulatory decision-making associated with sulfuryl fluoride. Detailed explanations are provided in this document, referenced by the RCD page number and section. Refined margins of exposure based on more accurate and realistic exposure scenarios and toxicity values are also presented.

SULFURYL FLUORIDE (VIKANE™ GAS FUMIGANT) USE PATTERN

Introduction

Sulfuryl fluoride (SF), the active ingredient in Vikane gas fumigant, is widely used for the control of dry wood termites (DWT). It is occasionally used (<2% of all treatments based on sales) to control other structural-infesting pests, such as wood-boring beetles (e.g. powder post beetles, PPB), cockroaches and rodents. Structures to be fumigated are typically sealed or enclosed with heavy nylon tarpaulins to confine SF, in order to maintain a maximum concentration and exposure within the fumigated structure. The structure generally remains sealed for approximately 18-24 hours followed by a minimum six to eight hour aeration period. During the aeration period, the tarpaulin is removed and the structure is initially actively aerated for a minimum of 1 hour with the use of natural ventilation and fans. The structure is then secured and passively aerated for the remainder of the six to eight hour period. Re-occupation into the fumigated structure by the resident is only permitted following this aeration period and after it has been confirmed that SF concentrations are at or below 5 ppm within the dwelling. If, at the end of the prolonged aeration period, ambient levels are measured at concentrations above 5 ppm, windows and doors are opened in the house for a second short period (a minimum of 10 minutes) at which point the SF concentrations are re-analyzed to determine whether SF concentrations are at or below 5 ppm prior to re-occupation.

Additionally, SF is occasionally used to control insect pests in shipping containers. This use occurs infrequently due to the existence of alternative fumigants such as methyl bromide and phosphine which have been specifically developed for this use.

Powder-Post Beetle Rate Calculations

When determining the appropriate scaling factor for adjusting potential exposure between those measured during the dry wood termite exposure studies (DWT fumigation rate is termed “submaximal” within the RCD) to those estimated for the control of PPB (SF uses rates termed “maximal” within the RCD) there are several factors to consider.

Vikane fumigations are based on the following concept.

DOSAGE (ounce hours) = CONCENTRATION (C) X TIME (T)

DWT fumigations generally target a CT in the range of 100 oz hr/1000 ft^3 CT and PPB fumigations target a 10x CT dosage or about 1000 oz hr/1000 ft^3. Therefore, if a non-monitored PPB fumigation was going to be conducted for the same fumigant holding period as a DWT treatment, the DWT dosage would be calculated using all appropriate inputs to the Fumiguide* B and then multiplied by 10x to calculate the PPB dosage.

Using a high concentration of fumigant could be cost prohibitive due to the amount of fumigant required for the PPB treatment. Fumigators overcome this challenge in several ways. A common practice is to extend the time component of the CT product function. Companies can also reduce the target dosage, and thus the amount of fumigant needed, by monitoring the fumigation and/or postponing the fumigation until a warmer time of the year. Lengthening the fumigant holding period reduces the amount of fumigant required to obtain the desired CT. A representative range of typical DWT and PPB fumigations is provided in the following table.

Typical Use Rates, Holding Times, and Terminal Concentrations for Termite and Powder Post Beetle Fumigations in California.

	Termite Rate (1x rate)	Beetle Rate (10x rate)
Oz Hr Objective (CT)	60-100 oz hr	600-1000 oz hr
Initial Conc.	4-16 oz/MCF	40-80 oz/MCF
Holding Time	20-24 hrs	36-48 hrs
Typical Terminal Conc.	1-4 oz/MCF	8 - 14 oz/MCF

A 10x rate is not reflected in the initial concentration, but in the combined initial concentration x holding time CT. It is noteworthy to point out that the terminal concentrations in the monitoring studies submitted by DAS to DPR were approximately 10-12 oz/MCF. The terminal concentration levels from the DAS studies are about the same as the typical terminal concentrations of PPB fumigations. Thus, applying a 10x factor to exposure scenarios to represent PPB rates is inaccurate and misleading.

Below are additional comparisons of typical DWT to PPB SF "concentration" calculations assuming an unmonitored job with a 14 hr half-loss time (HLT) and a 36 hr exposure period for PPB vs. a 24 hr exposure period for DWT fumigations.

Temperature	DWT Conc. 24 Hr. Period (oz/1000 ft^3)	DWT Conc. 36 Hr. Period (oz/1000 ft^3)	PPB Conc. at 10x the 36 Hr. DWT rate (oz/1000 ft^3)	PPB Terminal SF Conc. [a] (oz/1000 ft^3)
65 ºF	11.2	9.3	93	16
70 ºF	9.3	7.8	78	13
75 ºF	7.9	6.6	66	11
80 ºF	6.9	5.8	58	10

[a] Approximately 30% would be remaining after 24 hr exp and 14 hr HLT; approximately 17% would be remaining after 36 hr exp. and 14 hr HLT.

This table of possible rate calculations for DWT and PPB fumigations suggest that the initial concentrations for the typical PPB fumigation compared to the rates used in the exposure studies (average Worker Exposure Study rate ~ 11 oz/1000 ft^3 and Bystanders ~16 oz/1000 ft^3) are about 4x to 8x that of the studied DWT rates. Terminal concentrations calculated for the typical PPB study are about 1-1.3x of the terminal concentrations aerated during the Bystander studies. Therefore the appropriate scaling factor for adjusting potential exposures between those measured during the dry wood termite DWT exposure studies to those estimated for a PPB fumigation is between 1x and 8x with a mean scaling factor of approximately 3.4X.

This scaling factor would be less if the dosing efficiencies of monitoring, warmer temperatures, and 48 hour fumigations were practiced for the infrequent and higher priced PPB jobs. It is important to note that PPB fumigations rarely occur in California, and only represent approximately 2% of the overall Vikane structural fumigations.

Frequency and Duration of Exposures

Calculation of "short term", "intermediate term" and "annual" absorbed daily dose (ADD) values for residents should not be necessary given their infrequent and short duration exposures. Acute exposures are the most appropriate endpoint to use for residents based on the air dissipation data and fumigation practices. The dissipation data shows a rapid loss of SF prior to and after clearance of the houses. Air concentrations are virtually undetectable after 2 days, the estimates of air concentrations beyond 2 days are simply a result of the modeling exercise with built-in conservative factors. Actual measurements show that SF air concentrations are often below the limit of detection after 2 days.

It is inappropriate to assume that residents are exposed to SF via house fumigations annually. Houses are typically fumigated once in 10 to 20 years or at the time of resale. A typical fumigation is initiated by a home inspection preparatory to sale. Following fumigation, approximately 10 years are required before dry wood termite populations reach a noticeable level and require re-treatment. The likelihood that an individual would be resident in a fumigated house either the day after fumigation or more than once in 10 years is extremely low. Therefore, there should be no short term, intermediate term, annual, or lifetime exposures for residents following fumigation of houses with SF. Similarly, there should be no short term, intermediate term, annual, or lifetime exposures for bystanders.

Relationship between Toxicological Studies for Sulfuryl Fluoride and Actual Exposures

	Acute	Short-Term	Intermediate	Annual	Lifetime
Duration of Exposure (RCD)	1 to 2 days	Up to 14 days	Up to 13 weeks	Up to a year	Lifetime
Appropriate NOEL	300 ppm	100 ppm (2 week rabbit)	30 ppm (13 week rabbit)	20 ppm (2 year rat)	20 ppm (2 year rat)
Occupational	Yes	Yes	Yes	Yes	Yes
Residential (re-entry)	Yes	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Bystander	Yes	Not Applicable	Not Applicable	Not Applicable	Not Applicable

Frequency of house fumigations

An informal survey of fumigation companies was done to provide information on the frequency of house fumigations and the frequency of repeated fumigations on the same house. Four companies in Southern

CA were contacted that represent approximately 80% of house fumigations and provided responses to Dow AgroSciences. Based on responses below, coastal homes are more frequently fumigated than homes inland. This is presumed to be due to the greater humidity in the coastal region which is more conducive to termite colony development. A summary of survey results is given here:

Summary by company interviewed:

- Company 1: Estimates 10-12 yrs between fumigations of the same structure.
- Company 2: 8-10 yrs in coastal region, less often inland.
- Company 3: Estimates that houses are fumigated every 7-12 yrs in coastal areas, and 15-20 years inland.
- Company 4: Estimates that houses are fumigated every 15+ years.
- In summary, houses in California are not fumigated annually. Those that are fumigated are only fumigated every 7 to 20 years.

Non-food commodity fumigations

To help estimate potential exposures to container (non-food) fumigations, an informal survey of fumigators was conducted by Dow AgroSciences. This survey concludes that the potential exposure to bystanders is very low. Fumigations typically occur in industrial areas or shipyards with limited public access.

The companies contacted conduct shipping container and chamber fumigations as a primary portion of their business. Shipping container fumigation of durables is relatively less common than fumigation of perishables such as fresh fruits and vegetables. Fumigations of durables usually last for 18-24 hours. A chamber fumigation of durables is a rare event, being conducted for fumigation of furniture and other durable objects for control of beetles, termites, etc., or when container contents are required to be emptied from the container prior to fumigation (see Royal Fumigation). Sulfuryl fluoride is sometimes selected for chamber fumigations when potentially sensitive equipment or artifacts are involved. However, the companies contacted rarely use sulfuryl fluoride at this time; rather they use methyl bromide or phosphine. There are several reasons for this, including: a) methyl bromide and phosphine have broad food tolerances, b) phosphine can be easily applied when using solid formulations, and c) cost advantages. Also, some of these use patterns are considered to be Quarantine or Pre-Shipment, and thus are exempt from the Montreal Protocol mandated phase-out of methyl bromide. Sulfuryl fluoride is also not used to treat perishable commodities because it is phytotoxic to perishable commodities, including produce.

Summary by company interviewed:

- Company A: Shipping containers must be emptied prior to fumigation, apparently due to regulations in the East Coast states they work in. Contents are tarped, then fumigated. Fumigation of durables occurs 10 business days per year x 3 hours/day of potential exposure activities (introduction, initiating aeration, clearance) for a total estimate of only 30 hrs/yr. Other non-exposure activities (e.g. preparation) and off-fumigation-site activities (travel, paperwork, etc.) make up the rest of the 8 hr workday. On the other hand, they would be fumigating perishables with methyl bromide on a daily basis.

- Company B: Fumigating – 52 weeks/yr x 5 days/week x 8 hrs/day, both container and chamber fumigations. Vikane is rarely used; rather methyl bromide and phosphine are applied. Chambers are vacuum chambers, with no leakage possible unless the chamber is malfunctioning, which would be readily detected. Vacuum fumigation using methyl bromide is primarily for fumigation of perishables. For container fumigation, estimate is for 30 minutes per day when worker exposure to fumigant could occur (introduction, initiating aeration, and clearance). The remainder of day (7.5 hrs) is spent conducting other activities such as travel and site preparation.
- Company C.: Container and vacuum chamber fumigation split - 25% perishables (fruits and vegetables) 75% durables (usually dunnage). The company works 5 days per week all year, fumigators working 8 hrs/day. They estimate that introduction, opening, and clearance would occupy no more than 25% of the day. They do not normally use Vikane at this time because of the need to use chloropicrin.
- Company D: Container and vacuum chamber fumigation split – 80% perishables, 20% durables. Primarily 2 hr fumigations of perishables conducted at the port. Focus on import and export business. They typically work all year, 50 hrs/wk, 8-10 hrs/day. Estimated that potential exposure to fumigant time is 1.5 hrs/day during the introduction and aeration procedures. They seldom use Vikane because they are primarily fumigating perishables.

Structural Worker Exposure Duration and Frequency

Several CA fumigation companies were contacted by phone to determine the length of career as: a) a crew member, or b) licensee for structural fumigation. Generally, the career as a crew member (putting tarps on, removing tarps, etc.) is limited to an average of 5-10 yrs due to the demanding physical labor involved, relatively low wages, and advancement to managerial positions. Career duration of licensees generally averages 10-15 yrs, which is longer than crew members, because pay is higher and work is less physically demanding.

While fumigation workers may work 5 days/week, it is unlikely they work 52 weeks/year for their entire career as fumigators. Weeks not spent fumigating are spent on vacation/holidays and work activities unrelated to fumigation, particularly during the “slow season”. A more realistic estimation would be 48 weeks per year or less that would be spent actually engaged in fumigation activities.

DOSE/RESPONSE AND HAZARD IDENTIFICATION

Toxic Air Contaminant Considerations

The RCD specifies (*Page 69, V.D.2.b Reference Concentration)* "Based on criteria (1), the exposures estimated for many scenarios (Table 17-22) were higher than the reference concentrations based on an uncertainty factor of 100". The quotation from the RCD appears to be at odds with regulatory requirements for several reasons. The California Code of Regulations Title 3 Section 6890 sets forth criteria for identifying pesticides as toxic air contaminants. The regulation specifies "A pesticide shall be identified as a toxic air contaminant if its *concentrations* in ambient air are …ten-fold below the air *concentration* which has been determined by the director to be adequately protective of human health". First, Dow AgroSciences questions whether air on a work site is ambient air, i.e., we do not believe this regulation is intended to apply to workers. Secondly, a specific ambient air concentration for regulatory purposes is not identified (there are several with varying durations of exposure and it is not clear which is the defining criteria for AB 1807). Thirdly, air concentrations are not shown in Tables 17-22.

Epidemiology

The RCD **(***III.H.2. Occupational Exposure, page 38*) includes summaries of two studies of methyl bromide and sulfuryl fluoride fumigation workers in California (Anger *et al.*, 1986) and Florida (Calvert *et al*., 1998). Dow AgroSciences does not believe that either study demonstrates adverse health effects to fumigation workers.

Anger *et al*. (1986) suggest that their data argue "in favor of subjecting sulfuryl fluoride to further study." Given the absence of any statistically significant differences over about 70 endpoints, and the presence of small non-significant differences going in opposite directions (e.g., improved tactile sensitivity on one hand, vs. increased symptoms in lower extremities and decreased performance in cognitive tests on the other hand), and given the presence of confounders (participation bias, expectation bias) and the author's cautions in their discussion, the study **does not** support the statement that sulfuryl fluoride has any effects on any of the endpoints examined, including cognitive.

With regard to the paper by Calvert *et al***.** (1998), the results of this study of structural fumigant workers are better explained by bias, confounding or chance than by exposure to fumigants. This is especially true since the authors indicate that the exposure to sulfuryl fluoride, based on a 1991 NIOSH study, was non-detectable or below the Occupational Safety and Health Administration permissible exposure limits. Additionally, the study observed no more statistically significant positive findings than would be expected given the large number of comparisons made. In light of the above mentioned weaknesses and inconsistencies, the current study does not show an adverse health effect due to long-term low level exposure to sulfuryl fluoride.

Detailed comments for the two fumigation worker studies (Anger *et al.*, 1986; Calvert *et al*., 1998) are provided in the following sections.

Neurobehavioral Evaluation of Soil and Structural Fumigators Using Methyl Bromide and Sulfuryl Fluoride. Anger, W.K., Moody, L., Burg, J., Brightwell, W.S., Taylor, B.J., Russo, J.M., Dickerson, N., Setzer, J.V., Johnson, B.L. and Hicks, K. NeuroToxicol. 7: 137-156, 1986.

<u>Study summary</u>. Three groups of fumigators exposed to methyl bromide (N=32), sulfuryl fluoride (N=24) or to a combination of both (N=18) were compared to a referent group (N=29) composed of workers who had a job related to the fumigation industry, but were not directly exposed to fumigants on a regular basis (a chemist, fumigation tank fillers, salespeople, supervisors, owners and state specialists or inspectors). The subjects were examined blind to treatment; however, the blind procedure was not effective as reported by the authors (p. 142). The following functions/tests were evaluated: general symptoms, nerve conduction velocity/peroneal, grip strength, eye-hand coordination, nerve conduction velocity/ulnar, vibration sensitivity, tactile depth discrimination, two-point discrimination, electromyogram, eyeblink reflex, visual depth discrimination, Wechsler memory scale, digit symbol substitution, trailmaking, attention test. Fumigators using methyl bromide reported a significantly higher prevalence of symptoms consistent with toxicity than the control group, and did not perform as well as the controls on 23 of 27 behavioral tests. As far as the fumigators exposed to sulfuryl fluoride were concerned, they had slightly but not significantly decreased scores on some cognitive tests compared to the control group.

<u>Dow AgroSciences Comments</u>: Most of the fumigant workers used both methyl bromide and sulfuryl fluoride. The mean estimated use of sulfuryl fluoride by the methyl bromide group was 8% (see Table 3 of publication). However, no information is provided if *all* methyl bromide workers also used sulfuryl fluoride. The following analysis will focus only on the sulfuryl fluoride data.

The authors reported <u>no statistically significant difference between the control and sulfuryl fluoride exposed groups</u> for the following endpoints:

1. **Overall comparisons**
    a. symptoms
        i. Ss reporting one or more in past month
        ii. Ss reporting one or more since entering occupation
2. **General**
    a. symptoms
        i. muscle aching
        ii. muscle fatigue
        iii. coordination problems
        iv. depression

   v. slurred speech
   vi. dizziness

3. **Gait and station**
   a. symptoms
      i. stumbling when walking
      ii. weaving and staggering
   b. neurological exam
      i. walking
      ii. tandem walking
      iii. standing/eyes open
4. **Lower extremity/motor and reflexes**
   a. neurological exam
      i. walk on heels, toes
      ii. heel to shin
      iii. knee reflexes
      iv. ankle reflexes
   b. nerve conduction velocity/peroneal
      i. standardized nerve conduction velocity
      ii. standardized distal latency
5. **Lower extremity/sensory**
   a. symptoms
      i. tingling in feet
      ii. numbness in feet
   b. neurological exam
      i. standing/eyes closed
      ii. position sense in toes
      iii. vibration sense in toes
6. **Upper extremity/motor**
   a. symptoms
      i. muscle weakness in hands
      ii. hand tremor
   b. neurological exam
      i. grip strength
      ii. arms out/eyes closed (with drift)
      iii. write sentence
      iv. pronation/supination hands
      v. fingers/thumb
      vi. touch nose with forefinger
      vii. finger/nose/finger
      viii. arms out/eyes closed (with tremor)
      ix. biceps reflexes
      x. brachial/radial reflexes
   c. nerve conduction velocity/ulnar
      i. standardized nerve conduction velocity
      ii. standardized distal latency
   d. dynamometer
      i. grip strength
      ii. fatigue
   e. Michigan Eye-Hand coordination
      i. time to complete test
      ii. standard deviation of hole to hole time
7. **Upper extremity/sensory**
   a. symptoms
      i. tingling in hands
      ii. numbness in hands
   b. neurological exam

i. position sense/fingers
ii. vibration sense/fingers

c. optacon
   i. threshold
d. tactile depth discrimination
   i. threshold
e. two-point discrimination
   i. threshold

8. Visual signs and symptoms/extraocular movements

a. symptoms
   i. blurred vision
   ii. focus problems
   iii. eye twitches
   iv. wear glasses
b. neurological exam
   i. nystagmus
c. electromyogram
   i. amplitude
d. eyeblink reflex
   i. prepulse/baseline ratio amplitude
   ii. prepulse/high latency ratio
   iii. prepulse/low latency ratio
e. orthorater
   i. visual depth discrimination
   ii. acuity, far/worst eye
   iii. acuity, near/worst eye
   iv. acuity, far/both eyes
   v. acuity, near/both eyes

9. Cognitive effects

a. neurological exam
   i. objects recalling
b. Wechsler memory scale
   i. number of facts recalled
c. Digit symbol
   i. correct matches
d. trailmaking A
   i. time to complete
   ii. number of errors
e. trailmaking B
   i. time to complete
   ii. number of errors
f. Bourdon Wiersma
   i. correct strikeouts

The sulfuryl fluoride group had more symptom-positive reports in the lower extremities than the referents; however, it performed better than the referent group on all three tests of tactile sensitivity (i.e., vibration sensitivity, tactile depth discrimination and two-point discrimination). A statistically nonsignificant reduced performance in all cognitive tests was found in the sulfuryl fluoride group compared to the control group in the presence of a nonsignificant increase of illegal drug use and of drinks per week, and decrease in educational level in the sulfuryl fluoride group compared to the control group (see Table 4, page 146). The cognitive data are summarized in the table below. The magnitude of the differences between control and sulfuryl fluoride groups in these cognitive tests ranged approximately from a twentieth to a third of one standard deviation.

Cognitive Tests	Referent Group (Mean)	Sulfuryl Fluoride Group (Mean)	Referent Standard Deviation	Difference between means expressed in Referent Standard Deviations
Wechsler Memory Scale	21	19	7	0.29
Digit Symbol	58	54	12	0.33
Trailmaking A	27	28	9	-0.11
Trailmaking B	74	76	34	-0.06
Bourdon-Wiersma	286	279	39	0.18

The authors start their discussion by warning the reader about the lack of information concerning the participation bias that would have encouraged the workers who present medical problems to participate in the study (although they do not have any evidence for this). They continue warning the reader about "a welter of potentially biasing factors that cannot be satisfactorily unraveled." (p. 153), including expectation bias (i.e., the awareness of chemical exposure will result in over-reporting of symptoms and will cause the subjects to perform below their ability).

The 29 Referents were defined as employees of the fumigation company but not as active fumigators. Compared to the 24 sulfuryl fluoride fumigators, the Referents were older (mean age 36 vs. 31), better educated (96% vs. 86% had > 8 years), and used less illicit drugs and alcohol. The Referent group is known to have a more sedentary and less strenuous job than the structural fumigators (page 153). With these known differences, suggesting additional unmeasured differences, the Referent group is an inappropriate control group for this study. The results presented in Table 5 – 10 are crude means that do not represent data adjusted for the measured differences in the two groups. Uncontrolled differences reflect the underlying differences in the Referent group as shown in Table 4. When statistical adjustments were made, there were no significant differences between the sulfuryl fluoride fumigators and the controls.

The authors suggest that their data argue "in favor of subjecting sulfuryl fluoride to further study." (page 154). Given the absence of any statistically significant differences over about 70 endpoints, and the presence of small nonsignificant differences going in opposite directions (e.g., improved tactile sensitivity on one hand, vs. increased symptoms in lower extremities and decreased performance in cognitive tests on the other hand), and given the presence of confounders (participation bias, expectation bias, …) and the author's cautions in their discussion, we conclude that the study **does not** support the statement that sulfuryl fluoride has any effects on any of the endpoints examined, including cognitive.

Health Effects Associated With Sulfuryl Fluoride and Methyl Bromide Exposure Among Structural Fumigation Workers. Calvert G.M., Mueller, C.A., Fajen, J.M., Chrislip, D.W., Russo, J., Briggle, T., Fleming, L.E., Suruda, A.J., and Steenland, K. Amer J Public Health 88: 1774-1780, 1998.

Study summary. The Calvert *et al*. study is a cross sectional study of workers employed at the time of the study in the structural fumigation industry. Exposure to methyl bromide or sulfuryl fluoride was defined by the years employed and the percent of jobs in the past year using methyl bromide or sulfuryl fluoride. The referent subjects were friends or neighbors of the exposed subjects.

Fumigation workers performed worse on tests of median nerve function than did the referents. The authors attributed this finding to ergonomic stresses of the job. A trend of worse performance in Pattern Memory with increasing lifetime duration of sulfuryl fluoride was observed. A significant deficit of olfactory function as measured by UPSIT performance among the high sulfuryl fluoride exposed workers also was observed.

Dow AgroSciences Comments: The Calvert *et al*. study is a relatively large study of fumigant workers with good attention to study design, methodology and data analysis. The use of friend controls was appropriate for this mostly immigrant population. The data are presented well, and the tables in the paper are comprehensive, in that they show all the endpoints under study. However, there are some weaknesses to the study due to poor exposure determination, cross-sectional design, control of error rate and cultural sensitivity of the UPSIT.

The exposure measure for this study was a component of years worked in the fumigation industry and proportion of fumigation jobs that used methyl bromide (or sulfuryl fluoride). This is not a true indication of *exposure*. There is no distinction between *exposure* and *use*. In fact, the exposure measure is merely a marker for employment in a physical and potentially stressful job, which may completely explain the differences between the fumigation workers and referents. The authors state in their discussion section that the fumigant exposure among structural fumigation workers is low based on personal airborne sampling conducted by NIOSH in 1991. The NIOSH study showed that all personal airborne sampling results for sulfuryl fluoride were below the Occupational Safety and Health Administration permissible exposure limits (20 mg/m^3 {5 ppm}time-weighted 8-hour average). Furthermore, the NIOSH study showed that more than two thirds of the measurements were below the limit of detection for sulfuryl fluoride (0.007 mg/sample). Thus, the lack of significant or even measurable exposure of structural fumigation workers as represented by the NIOSH study suggests that the results of the Calvert et al. (1998) study should be attributed to factors other than sulfuryl fluoride.

The Calvert *et al*. study relies upon the differences between workers and referents in test performance on a single day. The study was not designed to determine if reductions in performance were pre-existing to the study period. The referent group was younger, more educated, fewer Spanish speakers, and consumed less alcohol and tobacco. These factors were adjusted in the statistical models. Since this study was cross-sectional, other pre-disposing, unmeasured differences between the groups may explain the differences in their neurobehavioral performance.

The authors controlled the Type I error rate at 0.05 per comparison. However, a large number of *p* values (about 115 *p* values) were derived, and there were 9 statistically significant *p* values. According to Gill (1985)[1], the minimum number of statistically significant tests (at alpha = 0.05) required for 95% confidence that a true difference exists for one or more out of 115 traits is 10, i.e. the 9 significant differences could simply be explained by the false positive rate associated with the total number of comparisons. If some statistically significant differences are deemed to be true positives due to an emerging pattern, for example, the case can be made that the effect is a true effect (the next question being whether the effect size has biological significance).

The authors correctly attribute the positive findings for the median nerve motor conduction velocity and Santa Ana dexterity test (preferred hand) to workplace ergonomic factors rather than exposure to the fumigants. The authors mention that the one median nerve outcome (nerve conduction velocity of the median motor nerve in the forearm) associated with exposure to sulfuryl fluoride "may be an isolated chance finding caused by the large number of comparisons that were performed."

Reduced performance on the Pattern Memory test appears to be the only positive finding of potential memory effects. However, the other endpoints related to memory are all negative for an association, i.e. Pattern Memory recall time, Symbol Digit, Symbol Digit recall score, Serial Digit Learning score. Thus, the observed effect is unlikely to be a *true* exposure-related effect. In fact, the authors state that "…the pattern memory findings may have arisen by chance."

Some comment on this test is warranted. The UPSIT is not a culture-free test. For example, pumpkin pie, gingerbread, wintergreen, chili, licorice, dill pickle and root beer are very much part of the US culinary armamentarium and culture. Some people with a higher education may more easily recognize musk, leather and cedar than people with only a few years of schooling. These odors were presented in the original test, as described in 1984.[2] While the exact odors of the UPSIT in the current study were not

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1 Gill. Interpretation of significance in testing multiple traits. J. Anim. Sci. 1985;60:867-869.

2 Doty et al. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol. Behav. 1984;32:489-502.

provided, differences in odor recognition among the study subjects may have more to do with acclimation to US culture than with exposure.

The study did not find significant associations with exposure for vibration testing, the NES vocabulary test, postural sway testing, and contrast sensitivity. Furthermore, measures of urinary total protein, albumin and adenosine deaminase binding protein were normal which suggest no effect on kidneys. Also, no significant differences were found between fumigation workers and referents for chronic bronchitis based on questions recommended by the American Thoracic Society.

The Calvert *et al*. study is a relational study. The investigators categorized subjects' sulfuryl fluoride exposure in relation to their methyl bromide exposure. In the context of understanding potential health risks from sulfuryl fluoride exposure, the results for the high methyl bromide exposed group are equally important because *all* of the high methyl bromide subjects were also 'exposed' to sulfuryl fluoride. For example, the two statistically significant deficits among the high-exposure sulfuryl fluoride workers, the olfactory test (UPSIT) and the pattern memory test, were marked by *better* performance among the high-exposure methyl bromide workers.

The results of Calvert *et al*. study of structural fumigant workers are better explained by bias, confounding or chance than by exposure to fumigants. This is especially true since the authors indicate that the exposure to sulfuryl fluoride, based on a 1991 NIOSH study, was non-detectable or below the Occupational Safety and Health Administration permissible exposure limits. Additionally, the study observed no more statistically significant positive findings than would be expected given the large number of comparisons made. In light of the above mentioned weaknesses and inconsistencies, the current study **<u>does not</u>** show an adverse health effect due to long-term low level exposure to sulfuryl fluoride.

Selection and Treatment of Proper Acute NOEL

The RCD (*V.B. Hazard Identification, pages 65-66*) indicates that the acute NOEL was selected from a 2-day inhalation study (6 hours/day) specifically designed to evaluate the neurotoxicity of sulfuryl fluoride. At the highest dose (300 ppm) tested, there were no treatment-related effects observed (Albee *et al*., 1993 a and b). The RCD notes that there is an issue in regard to the derivation of a one-day NOEL and the application of this NOEL for the MOE calculation. DPR calculates the NOEL for 24-hour exposure using the single day NOEL from the study, as shown below:

$$300\ ppm \times \frac{6\,hours}{24\,hours} = 75\ ppm$$

Dow AgroSciences agrees with the selection of the 2-day neurotoxicity study for the acute toxicity endpoint as well as the NOEL of 300 ppm for this study. However, DPR calculated a 24-hour exposure NOEL “using the single day NOEL from the acute study” but, in fact, the study design did not include any evaluations after the first exposure and thus, there was no basis for a single-day NOEL. Furthermore, the calculation of the dose-time relationship in the RCD significantly underestimates the relevant internal dose to the rats and thus underestimates the MOE for humans.

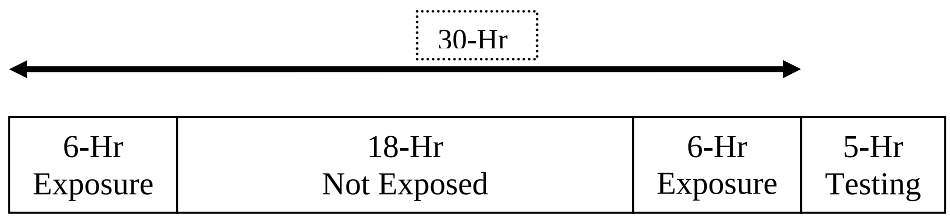
The two-day acute study was specifically designed to evaluate neurotoxicological end points immediately following the second of two daily exposures that were expected to result in a cumulative internal dose greater than a single 4-hr exposure. The acute NOEL of 300 ppm from the two-day, rat acute inhalation neurotoxicity study is appropriate for bystanders and also relevant to reoccupation of structures after clearance for reentry.

The acute neurotoxicity study was required in a November, 1992 Data Call-In by the U.S. EPA. The study protocol was designed jointly by Dow AgroSciences and the U.S. EPA (EPA Memoranda, July 31, 1992 and Oct 8, 1992, from L.J. Hansen, Health Effects Division to L. Rossi, Reregistration Branch) in order "...to provide more accurate NOELs for short-term exposure to sulfuryl fluoride."

Repeated, daily, inhalation exposures with sulfuryl fluoride result in elevation of serum fluoride as well as cumulative toxicity which differs from a single exposure. Repeated exposures of rabbits (6 hr/day, 5 days/wk) to 300 or 600 ppm sulfuryl fluoride for two weeks resulted in cerebral malacia (necrosis). Also, repeated exposures of rats to 300 ppm for 13 weeks results in vacuolation in the brain as well as clear electrophysiological changes in evoked potentials. Importantly, evoked potential changes were detectable in the absence of vacuoles in the rats exposed to 100 ppm. On the grounds that neurophysiological changes would be expected to precede neuropathological lesions, Dow AgroSciences and the U.S. EPA agreed to a modified acute neurotoxicity protocol to examine rats for functional changes from the cumulative effects of two, 6-hr exposures.

The modified acute neurotoxicity guideline study was intended to meet the objectives of the acute neurotoxicity testing requirements of the EPA neurotoxicity guideline (EPA, 1991). The EPA specified that the “Rats should be exposed to sulfuryl fluoride for 2 consecutive days, 6 hrs/day rather than the typical acute single 4 hr exposure.” The EPA’s rationale for the modified duration indicated that “Inhabitants of houses <u>may</u> be exposed to low levels of sulfuryl fluoride over 1 - 2 days…” and also "The proposed exposure period [6 hrs/day for two days] should provide a more reasonable estimation of risk from short-term exposure to sulfuryl fluoride than is presently available."

The study design for the two-day rat neurotoxicity study utilized an initial 6-hr exposure to sulfuryl fluoride, followed by 18-hr non-exposure, followed by a second 6-hr exposure to sulfuryl fluoride. Thus, there were two 6-hr exposures within a 30-hr time period. The critical neurotoxicological evaluations (electrodiagnostics and functional observational battery) were conducted within 5 hr after the second exposure. The electrodiagnostic evaluations were initiated 1.5 hrs post exposure and were completed by 4.4 hrs post exposure. The functional observational battery evaluations were initiated 0.7 hrs post exposure and completed by 1.4 hrs post exposure. The non-specific, less sensitive motor activity testing was initiated at 18 hrs post exposure and completed at 19 hrs post exposure.



Inherent in this cumulative-dose study design are the two, 6-hr exposures that occurred within a 30-hr (1.25-day) time period. Thus, the calculated internal dose of sulfuryl fluoride for the rats should be based on the total internal dose from both 6-hr exposures. The internal dose during the 30-hr (1.25-day) period was 708.7 mg sulfuryl fluoride/kg body weight based on the actual average body weight of 0.1435 kg for the rats on the study and an inhalation rate of 0.1626 m^3/day ($I = 0.80\ W^{0.8206}$; Blackburn, K. Recommendations for and Documentation of Biological Values for Use in Risk Assessment, ORD, U.S. EPA, Cincinnati, OH, EPA/600/6-87/008, 1988). This calculation assumes 100% absorption.

$$300\ ppm \times 4.17 \times \frac{0.1626\,m^3}{day} \times 1.25\,days \times \frac{0.5\,day\ exposure}{1.25\,day\ time\ period} \div\ 0.1435\ kg = 708.7\,mg/kg$$

The potential exposure to bystanders is consistent with the exposure scenario used in the two-day acute neurotoxicity study (Albee *et al.*, 1993). The data presented in the home fumigation study (Barnekow *et al.*, 2002) revealed that the potential exposure to bystanders occurs at two time intervals with a decline to low or no exposure between the two exposures intervals. The initial exposure interval was at fumigant introduction followed by a decline to background or near background levels within 8 hours. The second potential exposure occurs for approximately 2 hour at the initiation of aeration followed by an immediate drop to background (not detectable: ½ LOD = 0.01 ppm).

Since potential bystander exposures from fumigation and aeration occur within a 30-hr time period, the total exposure from the two-day acute neurotoxicity study is relevant and appropriate for bystander risk assessment. As indicated by the U.S. EPA (above), the 30-hr time period also is a reasonable surrogate for reoccupation of homes after clearance to very low levels of fumigant. The total internal dose to the rats from both of the 6-hr exposures within the 30-hr (1.25-day) exposure scenario was scaled to a 24-hr potential human exposure in order to correspond to the 24-hr time-weighted average data utilized for bystander exposure estimates (Wright et a*l*., 2003). Thus a more accurate NOEL determination for 24 hour exposure would be as follows:

708.7 mg/kg body weight/1.25 days = 567 mg/kg body weight/day

Recent research by the Neurotoxicology Division of NHEERL, U.S. EPA, indicates that internal tissue dose better predicts a constant biological effect than simple exposure concentration times duration and is thus more relevant for human risk assessment (Evans *et al*., 2002; Boyes *et al*., 2003). This appears to be especially true for short-term durations of exposure as compared to chronic exposures. The classic form of Haber's rule is a linear product: concentration multiplied by the exposure duration results in constant biological effect ($C \times t = k$). Haber's rule is widely used due in part to its mathematical simplicity and applicability to different chemicals and is often assumed to be applicable across different inhalation exposure durations. However, the recent EPA studies indicate that a traditional linear expression of Haber's rule was inadequate to predict neurotoxicity across exposure durations. A better predictor of toxicity is to understand the target tissue concentrations such as provided by, for example, physiologically based pharmacokinetic (PBPK) models.

Although PBPK modeling for sulfuryl fluoride is not available, Dow AgroSciences recently has completed and submitted to DPR an inhalation pharmacokinetic study (Mendrala *et al*., 2002). The results of the pharmacokinetic study suggest that sulfuryl fluoride toxicity is the result of metabolic release of fluoride ions. The data from the pharmacokinetic study and the repeated-exposure studies support the cumulative toxicological results from repeated, daily exposure to high levels of sulfuryl fluoride. In regard to the 2-day, acute neurotoxicity study, fluoride levels from the first 6-hr exposure, to some degree, would be expected to persist in some tissues for several hours following exposure. Thus, the internal dose of sulfuryl fluoride that results from both 6-hr exposures should be taken into consideration for the acute NOEL since both exposures would have contributed to any evidence of neurological effects.

Dow AgroSciences recommends that acute risk assessments utilize a NOEL of 300 ppm from the 2-day rat acute inhalation neurotoxicity study with an internal dose from both exposures (within a 30-hr time period) calculated at 708.7 mg/kg body weight. The relevant dose-time conversion for the 30-hr time period scaled to a 24-hr potential human exposure (correspond to the 24-hr time-weighted average data utilized for bystander exposure estimates) is 24/30 hr resulting in an internal dose NOEL of 567 mg/kg body weight per day.

References:

Boyes, W.K., Bercegeay, M., Ali, J.S., Krantz, T., McGee, J., Evans, M., Raymer, J.H., Bushnell, and Simmons, J.E. Dose-based duration adjustments for the effects of inhaled trichloroethylene on rat visual function, Tox. Sci. 76: 121-130, 2003

Evans, M.V., Boyes, W.K., Simmons, J.E., Litton, D.K., Easterling, M.R., A comparison of Haber's rule at different ages using a physiologically based pharmacokinetic (PBPK) model for chloroform in rats. Toxicology 176: 11-23, 2002

Mendrala, A.L., Markham, D.A., Clark, A.J., Krieger, S.M., Houtman, C.E. and Rick, D.L. Sulfuryl fluoride: Pharmacokinetics and metabolism in Fischer 344 rats, May 22, 2002.

Calculations from No-Observed Effect Levels (NOEL)

Dosage Normalization:

The RCD is inconsistent in normalizing animal exposure vs. human exposure. HS-1834, Appendix D-7 provides the calculation for the reference concentration in ppm. The reference concentration is calculated by first determining the human equivalent NOELs by the following equation. This equation includes the normalization of the exposure to 7 days (number of days exposed/7 days a week). If normalization is needed in the conversion of animal NOELs to human NOELs for short term, subchronic and chronic potential exposures then the two terms used in the conversion of the NOELs must be accounted for in the calculation of exposure estimates.

$$ADD = \frac{AD_i \times daily\ duration\ (hr/day) \times days\ \ potentially\ \text{exposed}\ (days/week)}{7\ (days/week) \times body\ weight\ (kg)}$$

$$MOE = \frac{NOEL\ (mg/kg/day)}{Human\ Exposure\ (mg/kg/day)}$$

Example Calculations:

(Fumigators worker – HS-1834, pp. 26-28, Tables 5, 6 and 7a)

Short-term = Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)}{7\ (days/week) \times 70\ kg} = 0.0046\ mg/kg/day$$

MOE = (40 mg/kg/day) ÷ (0.0046 mg/kg/day) = 8,695

Subchronic = Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)}{7\ (days/week) \times 70\ kg} = 0.0046\ mg/kg/day$$

MOE = (12 mg/kg/day) ÷ (0.0046 mg/kg/day) = 2,608

Chronic = Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)\ 208\ (days/year)}{7\ (days/week)\ 365\ (days/year) \times 70\ kg} = 0.00026\ mg/kg/day$$

MOE = (16 mg/kg/day) ÷ (0.00026 mg/kg/day) = 61,538

Lifetime= Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)\ 208\ (days/year)\ 40\ (working\ years)}{7\ (days/week)\ 365\ (days/year) \times 70\ (years\ lifetime) \times 70\ kg} = 0.00015\ mg/kg/day$$

MOE = (16 mg/kg/day) ÷ (0.00015 mg/kg/day) = 106,667

Calculation of Reference Concentration:

The RCD (*Appendix D*) provides the method for calculating the reference concentration; first by determining the dosage in animals equivalent NOEL and the secondly by determining the dosage in humans (specifically children). Using the child specific respiration rate adjusts for the difference in inhalation rate to body weight ratio differences between species. This specific correction for children is appropriate for exposure scenarios in which children are potentially exposed (acute exposures to the fumigation or re-entry of an aerated structure), but the calculation of the reference concentration using a child-specific respiration rate is not applicable to durations of exposure that do not exist for the child, i.e., short term (in this case 2 week), intermediate term and annual.

Mammalian Pharmacokinetics and Metabolism (ADME)

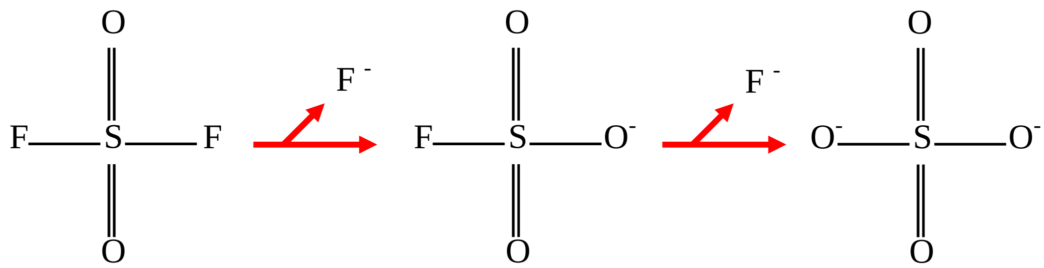
The RCD (*Toxicology Profile, page 14, paragraph 1*) states "There are no pharmacokinetic studies…" In response, it is important to point out that Dow AgroSciences recently has completed and submitted to DPR an inhalation pharmacokinetic study by Mendrala *et al.*, 2002. Overall, the metabolism study indicates a lack of systemic exposure to sulfuryl fluoride and indicates that the systemic toxicity of this fumigant is due to fluoride. The pharmacokinetics and metabolism of inhaled SO_2F_2 were evaluated in male Fischer 344 rats exposed to 30 or 300 ppm ^{35}S-labeled SO_2F_2 for 4 hr. Blood, urine and feces were collected during and after the exposures and analyzed for radioactivity as well as ^{35}S-labeled fluorosulfate and sulfate, and fluoride (urine and feces only). Selected tissues were collected 7 days post-exposure and analyzed for radioactivity. In addition, during and after exposures to unlabeled SO_2F_2, blood, brain and kidney were collected and analyzed for fluoride ion.

SO_2F_2 was rapidly absorbed via inhalation exposure, achieving maximum concentrations of radioactivity in both plasma and red blood cells (RBC) near the end of the 4 hr exposure period. Radioactivity was rapidly excreted, mostly via the urine as fluorosulfate and sulfate. Seven days post-exposure, small amounts of radioactivity were distributed among several tissues, with the highest concentration detected in respiratory tissues. Radioactivity associated with the RBC remained elevated 7 days post-exposure and highly perfused tissues had higher levels of radioactivity than other non-respiratory tissues. The radioactivity present in tissues suggests some incorporation of the ^{35}S via normal sulfate pool metabolism. Radioactivity cleared from plasma and RBC with initial half-lives of 2.5 h after 30 ppm and 1-2.5 h after 300 ppm exposures. The terminal half-life of radioactivity was 2.5-fold longer in RBC than plasma.

Sulfuryl fluoride is rapidly removed from rat blood fortified *in vitro* with high levels of sulfuryl fluoride ($t_{½}$<3 min) and is rapidly hydrolyzed in aqueous solutions ($t_{½}$<18 min at pH=8.0). Thus, no parent sulfuryl fluoride in blood or urine would be expected due to rapid hydrolysis. Based on the radiochemical profiles in the ADME study, there was no evidence of parent ^{35}sulfuryl fluoride in the blood. Identification of fluorosulfate and sulfate in blood and urine suggests that sulfuryl fluoride is hydrolyzed to fluorosulfate, with release of fluoride, followed by further hydrolysis to sulfate and release of the remaining fluoride. This metabolism is supported by the increases in fluoride detected in the blood and urine following exposure of rats to sulfuryl fluoride. The sulfuryl fluoride ADME study supports the hypothesis that sulfuryl fluoride toxicity is the result of metabolic release of fluoride ions rather than a direct toxic action of sulfuryl fluoride.

Key conclusions from the metabolism study are as follows:

- No measurable parent sulfuryl fluoride would be expected in blood or urine due to rapid hydrolysis.
- Inhaled sulfuryl fluoride is hydrolyzed to fluorosulfate and ionic fluoride followed by further hydrolysis to sulfate and an additional fluoride ion:



- Fluoride ion was rapidly excreted in the urine.
- No indication that sulfuryl fluoride, fluorosulfate, or fluoride bioaccumulate in soft tissues following inhalation exposure to sulfuryl fluoride.
- The data suggest that the systemic toxicity elicited by sulfuryl fluoride is due to the release of fluoride ions, rather than a direct toxic action of sulfuryl fluoride.

An absorbed dose was estimated based on measured internal dose from radioactivity as compared to internal dose estimated from inhalation rate and body weight. The estimated absorbed dose was 14.1% or 12.4%, respectively, for exposure concentrations of 30 ppm and 300 ppm. However, internal dose calculations for purposes of risk assessment were based on the default of 100% absorption.

In summary, the metabolism study of sulfuryl fluoride indicates a lack of systemic exposure to sulfuryl fluoride due to rapid hydrolysis. The data also suggest that the systemic toxicity of sulfuryl fluoride is due to the release of fluoride ions rather than a direct toxic action of sulfuryl fluoride. Thus, risk assessments related to the restricted use patterns and relatively low levels of potential human exposure to sulfuryl fluoride gas would be similar to the available evaluations for fluoride.

<u>Reference:</u>

Mendrala, A.L., Markham, D.A., Clark, A.J., Krieger, S.M., Houtman, C.E. and Rick, D.L. Sulfuryl fluoride: Pharmacokinetics and metabolism in Fischer 344 rats, May 22, 2002.

Dose Calculations based on 2-Generation Rat Reproduction Study

The RCD (*Reproductive Toxicity, page 34*) states that “Sprague-Dawley rats (30/sex/group) were exposed to sulfuryl fluoride (purity 97.32% ; 0, 5, 20, or 150 ppm) by inhalation (6 hours/day, 5 days/week) in a 2-generation study.”

DPR indicates that the NOEL of 5 ppm for the two-generation reproduction study is based on increased alveolar macrophages in the lungs of rats exposed to 20 ppm. Risk assessments must take into consideration that the rats on the reproduction study actually were exposed for 6 hours/day, **7 days/week during mating, gestation and lactation** through two generations.

Chronic NOEL Selection and Effects

The RCD states **(***IV.A.2.d. Chronic Toxicity*.) “The critical NOEL was 4 mg/kg/day (5 ppm) in rats for dental fluorosis in a chronic toxicity study (Quast *et al*., 1993a; Table 10) and for lung pathology and alveolar macrophage aggregates in a 2-generation reproductive toxicity study (Breslin *et al.*, 1992; Table 14). This critical NOEL was supported by a similar NOEL of 6 mg/kg/day (20 ppm) for similar pulmonary findings in dogs (Quast *et al.*, 1993c; Table 12)…For the purpose of this risk assessment, respiratory system effects were considered the critical effect for chronic inhalation exposure of sulfuryl fluoride.”

Dow AgroSciences believes the selection of toxic endpoints and the resulting selection of a chronic NOEL as described in the RCD do not accurately reflect the effects of chronic exposure to SF. The increase in alveolar macrophages is a manifestation of the irritancy properties of sulfuryl fluoride to the respiratory tract which is a portal of entry effect rather than a systemic effect. In contrast to the increase in alveolar macrophages in the lungs of rats exposed to 20 ppm for 7-days/week for 4-5 months on the reproduction study, lungs of rats, mice or dogs exposed to 20 ppm sulfuryl fluoride 5 days/week for 12, 18 or 24 months did not have alveolar histiocytosis or other effects. Since 5-days/week exposures more closely approximates the potential human exposure for workers, the NOEL of 20 ppm from the chronic studies with rats or dogs is more appropriate for repeated-exposure risk assessments.

Dental fluorosis in humans is detected by clinical examination. On the other hand, macroscopic dental fluorosis was not evident in either the 1-year dog or the 2-year rat study at any dose level during in-life phases or at necropsy. In the 1-year dog study, macroscopic dental fluorosis was not visible to the naked eye during the in-life phase or at necropsy at any dose level, including the high level of 200 ppm. However, histological examination of teeth revealed very slight or slight, microscopic concentric rings in the canine teeth that stained slightly darker and corresponded with each day of exposure at 80 and 200 ppm. As the teeth reached maturity it was more difficult to recognize the presence of the rings. These microscopic changes were not evident at 20 ppm.

In regard to the dental fluorosis in rats from the chronic toxicity/oncogenicity study (Quast et al., 1993), the Medical Toxicology Branch “Summary of Toxicology Data, Sulfuryl Fluoride” states that “Since the fluorosis is considered as a biomarker of exposure rather than as an adverse effect, a practical NOAEL is 20 ppm…” Also noted in the review is the fact that the U.S. EPA placed the NOEL at 20 ppm for this study.

Dow AgroSciences agrees that 20 ppm is the appropriate value to consider for chronic exposure risk assessments.

In the 2-year rat study, macroscopic dental fluorosis was not visible to the naked eye during the in-life phase or at necropsy at any dose level, including the high-dose level of 80 ppm. After formalin fixation, repetitive pale and slightly darker colored horizontal lines became evident on the labial surface of incisor teeth at 80 ppm; this change was never visible at 20 ppm, even after fixation. Microscopic dental fluorosis was diagnosed at 20 and 80 ppm. The dental fluorosis of the incisor teeth of rats was detected microscopically as basophilic lines in dentin and enamel in the incisor teeth. There was no significant change in ameloblasts, odontoblasts or dental pulp. The microscopic changes in the incisors were not detected in the molars. These findings are consistent with the fact that only the incisor teeth of rats erupt continuously during life and are maintained at a constant length by attrition of the occlusal surfaces. Total renewal of rat incisors normally occurs approximately every 40 to 50 days. Therefore, during the course of the 24-month study the incisor teeth were renewed approximately 15 to 18 times without significant clinical dental problems in any group. Although several male rats (12%) in the 20 ppm group had very slight microscopic change in their teeth (‘few, barely visible darker-stained concentric rings’), this effect is considered a biomarker of fluoride exposure in the rat and not an adverse effect.

Dental fluorosis of rodent incisor teeth is an inappropriate model for humans since rat incisor teeth continue to grow throughout adult life. Thus, fluoride-related dental changes in the continually erupting incisor teeth of rats on chronic toxicity studies are not relevant for human risk assessment.

Humans are not susceptible to dental fluorosis after 6-8 years of age (susceptibility is only during preeruptive development of teeth). Adult fumigation workers are not susceptible to dental fluorosis and thus, this end point is not relevant to chronic risk assessments. Although children ≤ 6-8 years of age could be considered for bystander and re-entry exposure assessments, these potential exposures are occasional (once every ~10 years) as well as transient (possibly minutes to hours for bystanders) or acute (1-2 days for re-entry). Furthermore, bystander and re-entry exposures are limited to very low levels of sulfuryl fluoride. Therefore, dental fluorosis is not a realistic possibility as a result of occasional, transient, low-level inhalation exposures to sulfuryl fluoride.

Low levels of fluoride intake are considered safe and health protective. In 1993 the National Research Council concluded that the EPA's Maximum Contaminant Level (MCL) of 4 mg/L for fluoride in drinking water continued to be appropriate as an interim standard. These governmental standards were set after extensive review of fluoride toxicological, medical, dental and epidemiological data that included consideration of infants and children as well as all sources of human fluoride exposure (World Health Organization, 1984; U.S. Public Health Service, 1991; National Research Council, 1993).

The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (DRI Committee, 1997) provides a consistent and coherent definition of requirements and reference intakes for all essential nutrients and food components. The DRI Committee established an Adequate Intake (AI) level for beneficial effects of fluoride.

The DRI Committee (1997) evaluated the relationship among dental caries experience, dental fluorosis index and the fluoride concentration in drinking water. The Committee concluded that:

"…reduction in the average number of dental caries per child was nearly maximal in communities having water fluoride concentrations close to 1.0 mg/liter. This is how 1.0 mg/liter became the "optimal" concentration. That is, it was associated with a high degree of protection against caries and a low prevalence of the milder forms of enamel fluorosis. The average dietary fluoride intake by children living in optimally fluoridated communities was (and remains) close to 0.05 mg/kg/day (range 0.02 to 0.10 mg/kg/day…)"

The value of 0.05 mg fluoride/kg body weight/day and appropriate reference weights for each age group were used by the DRI Committee to establish AI values (amount needed for prevention of dental caries) for fluoride. Thus, 0.05 mg/kg body weight/day is considered as adequate intake of fluoride for all age groups.

The DRI Committee regarded enamel fluorosis as a cosmetic effect on the teeth of children. Because the cosmetic effects of the milder forms of enamel fluorosis are not readily apparent, moderate enamel fluorosis was selected as the critical effect for susceptible age groups. Enamel fluorosis is a dose-response effect caused by fluoride ingestion during the preeruptive development of the teeth. The pre-eruptive maturation of teeth is completed by 8 years of age and the teeth are no longer susceptible to fluorosis. Thus, a fluoride intake of 0.10 mg/kg body weight/day was identified as a LOAEL for moderate enamel fluorosis in children from birth through the age of 8 years.

References:

National Research Council (1993). Health Effects of Ingested Fluoride. National Academy Press, Washington, D.C.

U.S. Public Health Service (1991). Review of Fluoride, Benefits and Risks. Department of Health and Human Services.

DRI Committee (1997). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academy Press, Washington, D.C.

World Health Organization (1984). Environmental Health Criteria 36, Fluorine and Fluorides. World Health Organization, Geneva.

Evaluation of Neurotoxicity Endpoints

Within the RCD, (*IV.A.1.a. Neurotoxicity, page 40, 1st paragraph and 3rd paragraph*), comments include a discussion of general neuropathology as well as findings for chlorfenapyr insecticide/miticide and reference to spongiform encephalopathies. The information on chlorfenapyr, spongiform encephalopathies and vaculated neurons in aged rats is interesting, but is not relevant to sulfuryl fluoride. This inferential speculation should not be included or considered within the DPR assessment.

In the comments on the long term and functional consequence of sulfuryl fluoride neurotoxicity, the RCD should include the findings and perspective provided by the evaluation of the recovery animals after 13 weeks of exposure as described in the report by Mattsson et al., 1986. Briefly, this study found that inhalation exposure of male and female Fischer 344 rats to sulfuryl fluoride at 300 ppm for 6 hr/day, 5 day/week for 13 weeks caused diminished weight gain, dental fluorosis, a slight decrease in grooming, slowing of visual, auditory and somatosensory-evoked potentials, mild pulmonary inflammation, and mild vacuolation in the brain. Auditory brainstem responses (ABR's) and brain histopathology were evaluated two months post-exposure in 2 male and 2 female rats. Both the ABR's and brain histopathology appeared normal at this time, indicating that these treatment effects were essentially reversible. Exposure to 100 ppm resulted in dental fluorosis and very minor slowing of some evoked responses; all other measurements, including brain histopathology, were normal. The NOEL was 30 ppm.

References:

Mattsson, J.L., Albee, R.R., Eisenbrandt, D.L., Nitschke, K.D. Neurological Examination of Fischer 344 Rats Exposed to Sulfuryl Fluoride (Vikane* Gas Fumigant) for 13 Weeks. Unpublished report of The Dow Chemical Company, Midland, Michigan. Report Date: 11/12/1986.

Note: This study was also published as Mattsson, J.L., Albee, R.R., Eisenbrandt, D.L., and Chang, L.W., Subchronic Neurotoxicity in Rats of the Structural Fumigant, Sulfuryl Fluoride, Neurotoxicology and Teratology, 10(2), 127-133, 1988.

Respiratory Effects

The RCD (*IV.A.1.b. Respiratory System Effects, page 42, 1st paragraph*) states "Respiratory tract effects were also reported in humans after accidental or intentional acute exposures." Information from postmortem examination of humans after accidental or intentional acute exposures to fumigation levels of sulfuryl fluoride (most likely, >10,000 ppm) is not relevant to low levels of potential worker, reentry or bystander exposure. This information is not appropriate for the weight-of-evidence evaluation.

EXPOSURE ASSESSMENT

Aggregate Exposure Assessment

Quoting from the RCD (*Page 69, V.E.2 Aggregate Exposure, Page 70 V.E.3 Cumulative Toxicity*) "There could be aggregate exposure of SF and fluoride from multiple exposure routes…". There is no mandate to aggregate non-pesticidal sources of exposure in a manner analogous to the U.S. EPA's Food Quality Protection Act. Although CDPR has been conducting aggregate risk assessments on pesticides for many years for pesticides, US EPA has only been doing this type of assessment since passage of the Food Quality Protection Act in 1996. However, even with a legislative mandate, FQPA is limited to pesticidal sources of a particular chemical. We question CDPR's legislative and regulatory authority to discuss or plan to conduct risk assessments on sources of fluoride that are non-pesticidal in origin. In so much as Dow AgroSciences has no control over pesticidal sources that it does not register (such as cryolite), natural sources of fluoride, or exposure to fluoride from dental hygienic uses including addition to drinking water, we find CDPR's statement regarding cumulative toxicity of fluoride-generating compounds inappropriate in this pesticide-specific risk assessment. We also find it contradictory that OEHHA, a sister Department in Cal EPA, has set a MCL for drinking water that allows chronic fluoride exposures orders of magnitude greater than any that might be experienced by residents/bystanders from structural, commodity or food stuff fumigation using SF, raising questions of regulatory consistency.

Correction of Air Monitoring Results

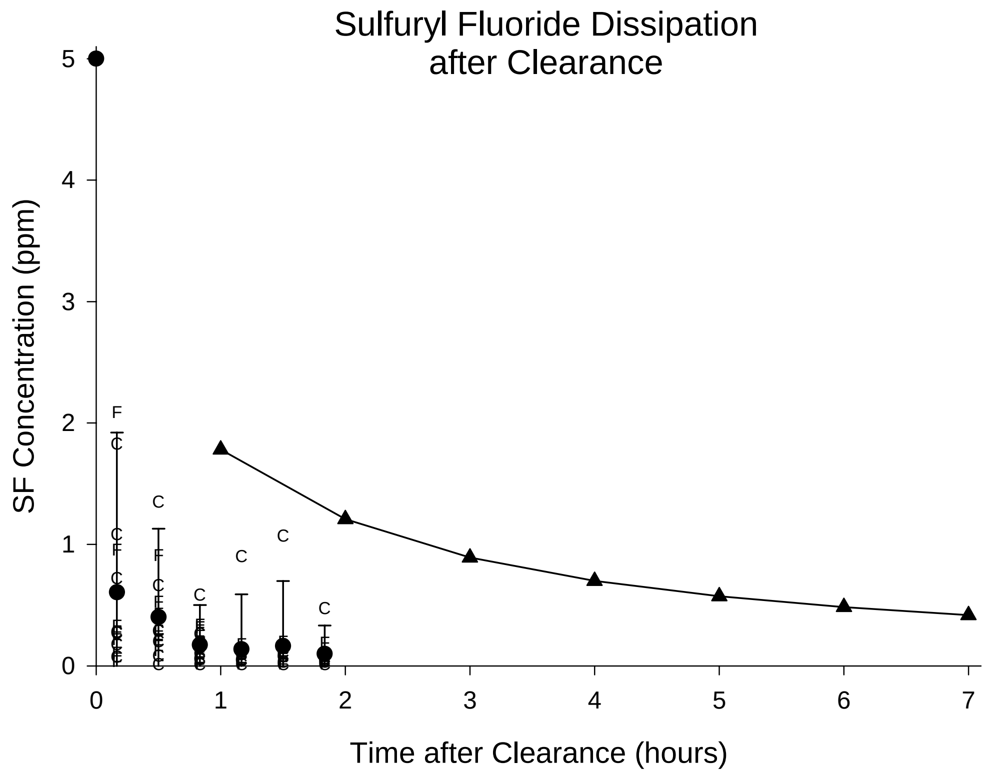
In Appendix C of the RCD (*HS-1834, page/line 19/31 to 20/7 and 24/4 to 24/10*), exposure values reported in Contardi and Lambesis (1996) were recalculated using the analytical recoveries from Huff and Murphy (1995) exposure study report to account for differences in the recovery values between the two studies. Both studies were amended to correct a negative-bias that was identified in the way the method was conducted. The amended reports both use nominal fortification levels to calculate recoveries. Therefore, the recovery data developed within each study is valid for that study. A recalculation of the air concentration values to correct for a lower recovery from a different study is inappropriate, air concentration levels should be corrected only by the legitimate study recoveries reported for that individual study when provided as part of the sample analysis. The Contardi and Lambesis (1996) study contains appropriate recovery values. The risk assessments developed from the Contardi and Lambesis (1996) should utilize the data presented in the reported and not values that have been artificially inflated by the application of recovery correction factor from a different study.

Calculations and Estimations of Residential Re-Entry Air Concentrations

The "best fit" mathematical function was not used to establish the post-clearance air concentration decay rate to calculate longer term re-entry exposure potential (*Appendix C. HS-1834, pg 33*)

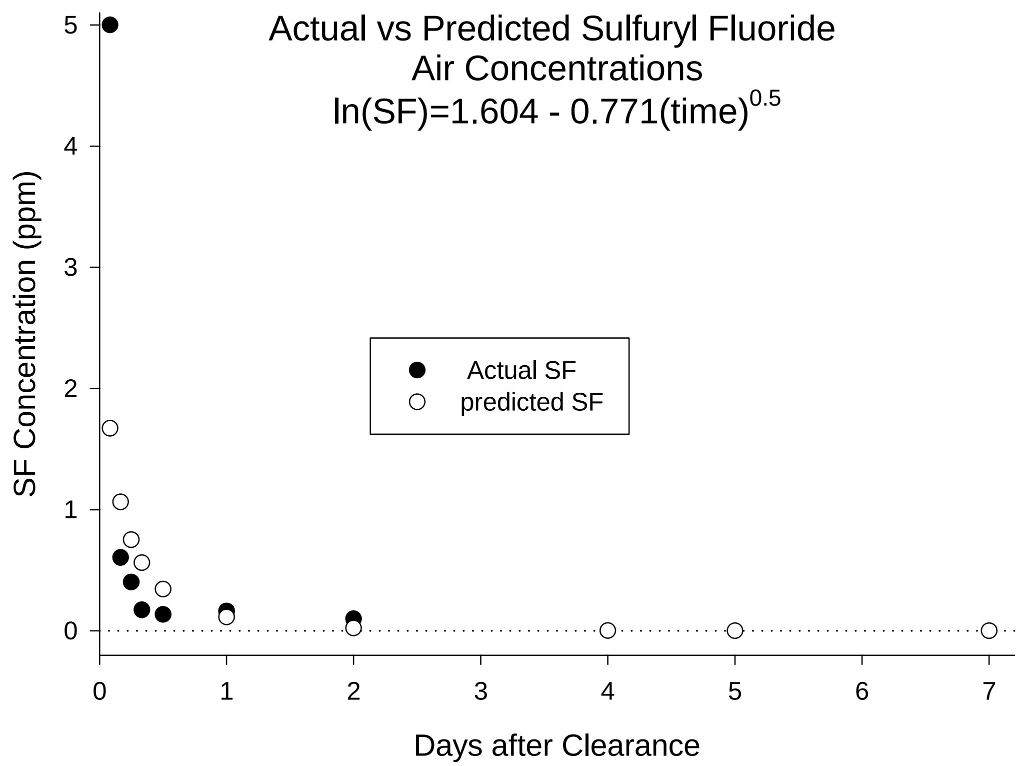
In establishing a model to estimate post-clearance air concentration decay rate to calculate longer term re-entry exposure potentials six models were evaluated. Three log-linear and three log-quadratic models were compared. Only small differences in R^2 were determined for like termed log-linear and three log-quadratic models indicating very little additional predictability by going to a log-quadratic function. On the other hand a significant increase in predictability was gained (increase in R^2) when additional terms, such as "House main effects", was added to the Hr term. Model 2, draft HS-1834, pg 34, was identified as the best and simplest model that accounted for most of the variance that can be accounted for by any of the models evaluated. Therefore, model 2 should be utilized for estimate post-clearance air concentration decay rate to calculate longer term re-entry exposure potentials.

We do not understand several aspects of the exposure calculations as presented. In the calculations, the air concentrations presented in the Shurdut report are adjusted for a recovery factor of 64.6%. However, the data within the Shurdut report were already corrected by a method recovery of 90.6% and a field recovery spike of 64% as appropriate for the study. The study presented data from 14 houses fumigated in California and Florida. The data for all the sites are shown in the following Figure 1 and compared to the 95%tile air concentration values as calculated by CDPR. As can be seen, there appears to be no difference between the air dissipation rates for houses in California (C) vs. Florida (F). The error bars represent the upper 95%tile confidence limit calculated for the combined data at each time point. While differences in aeration procedures exist between California and Florida, there appears to be no quantifiable difference in the resultant dissipation of the SF from the fumigated homes. The aeration practices have no influence on the resulting dissipation once the building is cleared for re-entry. In the following analysis, the results from the California and Florida houses were combined.



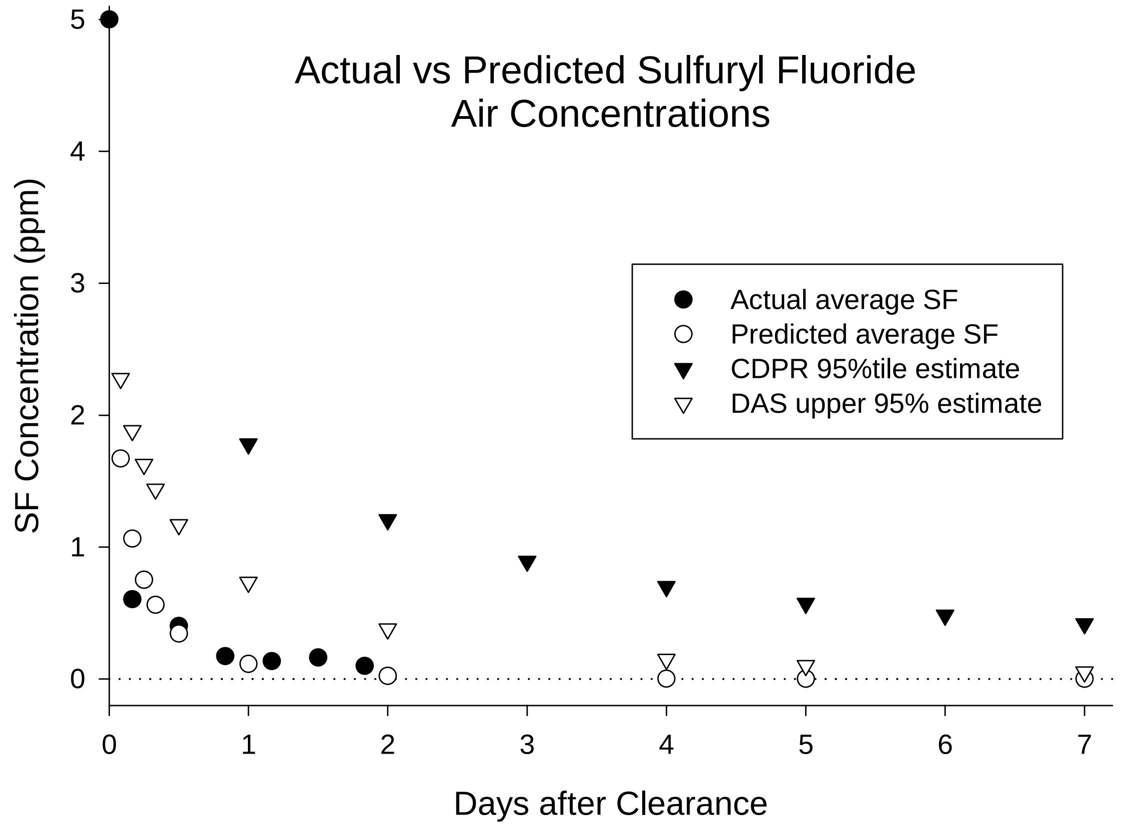
Measured vs. Predicted SF concentrations in treated houses after clearance to 5 ppm. Data from houses in California (C) and Florida (F) were combined. The house average data (•) plus 2 standard deviations (95%tile) are compared to the 95%tile, upper bound estimates used by CDPR (▲-▲).

The methods used to estimate the SF dissipation following clearance are not clear. The method as presented appears more complex than necessary and over-estimates the air concentrations. The data can be adequately modeled using the means at each time point as shown in the following figure except for the consistent over-estimation at times less than 1 day. The air concentration at time zero was assumed to be 5 ppm, the clearance value at the time of the study and most likely contributes to the discrepancy at times less than 1 day.



Actual vs. predicted air concentrations.

Of the many possible fits available in Table Curve 2D version 5.01, a reasonably simple form was chosen. As can be seen the equation given tends to over-estimate the air concentrations measured at less than 1 day but approaches zero much quicker than the CDPR estimates, and much closer to the data presented in the Shurdut report. Predictions of the upper 95%tile air concentrations were similarly obtained by fitting a curve to the individual, calculated upper 95% confidence limits for each measured time frame. This method better represents the confidence around the actual air measurements rather than the confidence around the fitted curve as presented by CDPR. A comparison of the two results is given in the figure and table below.



Comparison between the average measured vs predicted average air concentrations, and the upper 95% confidence limits calculated by DAS and CDPR.

Predicted air concentrations (ppm)		
	SF (ppm)	
Days	Average *	Upper 95% **
0	5	ND***
0.25	0.75	1.63
0.5	0.34	1.71
1	0.11382	0.73
2	0.02381	0.38
4	0.00261	0.15
5	0.00107	0.10
6	0.00048	0.07
7	0.00023	0.05

* Mean SF air concentration calculated by: $\ln(SF) = 1.6\text{-}4 - 0.77\ (time)^{0.5}$

** Upper 95% air concentration calculated by: $\ln(SF) = 1.283 - 0.325\ (time)^{0.5}$

*** The air concentration at time zero was defined as 5 ppm, the clearance value

A comparison between the values calculated by CDPR (tables 11 and 12) and DAS is provided below:

Air concentrations, integrated over time, for residences following clearance of homes to 5 ppm SF, CDPR vs DAS estimates.				
Post Clearance Interval (days)	CDPR average	DAS average *	CDPR Upper 95% tile	DAS Upper 95%tile *
0-1	0.436	0.419	1.781	1.13
0-2	0.298	0.237	1.208	0.83
0-3	0.216	0.163	0.893	0.65
0-4	0.166	0.123	0.700	0.53
0-5	0.133	0.099	0.573	0.452
0-6	0.111	0.082	0.484	0.392
0-7	0.095	0.07	0.418	0.34

* calculated as the area under the curve at each time point (Table 1) divided by the number of days.

According to the published CDPR policy[1], upper confidence limits should only be used for short term assessments, i.e., exposures of less than 7 days duration. Using these values over- estimates potential exposures because they fail to incorporate activity levels and varying amounts of time spent in the home. A more appropriate method is to amortize the exposures based on time weighted averages with adjustment for the amount of time actually spent in the home.

Selection of Proper Indicator of Central Tendency

Because the exposure monitoring results are typically skewed log-normally based on a statistical test for normality, the appropriate central tendency statistic should be the geometric mean. Further, when examining a large number of repeated measurements of individual and between individual exposures to pesticides, it is clear that intra-individual variability is greater than inter-individual variability so that the population mean is a more meaningful indicator of an individual's average daily exposure than any given daily measurement (Kromhout and Vermeulen, 2001).

US EPA's Scientific Advisory Panel summarized the conclusion well with the following quote. "When inflated "central tendency" values are put into the deterministic exposure calculation, they can be expected to overestimate the expected or "central tendency" exposure. If the distribution of exposure is highly

[1] Memo. October 4, 2001. Chuck Andrews, Chief, Worker Health and Safety Branch to Gary Patterson, Chief, Medical Toxicology Branch. WORKER HEALTH AND SAFETY BRANCH POLICY ON THE ESTIMATION OF SHORT-TERM, INTERMEDIATE-TERM, ANNUAL AND LIFETIME EXPOSURES. HSM-01014.

positively skewed, this bias may be considerable. In some cases the arithmetic mean values are substantially skewed and should be replaced by median values as a better indicator of central tendency. Working with high end values will be even worse, as the result will correspond to the very rare event of an exposure that is extreme in every respect and hence will be higher than is ever observed in reality.” (FIFRA SAP December 12, 2001).

ACGIH is quoted in the Introduction to the Chemical Substances TLVs:

> “The approach here is that the maximum recommended excursion should be related to the variability generally observed in actual industrial processes. In reviewing large numbers of industrial hygiene surveys conducted by the U.S. National Institute for Occupational Safety and Health, Leidel et al. (1975) found that short-term exposure measurements were generally lognormally distributed.
>
> While a complete discussion of the theory and properties of the lognormal distribution is beyond the scope of this section, a brief description of some important terms is presented. The measure of central tendency in a lognormal distribution is the antilog of the mean logarithm of the sample values. The distribution is skewed, and the geometric mean (m_g) is always smaller than the arithmetic mean by an amount that depends on the geometric standard deviation. In the lognormal distribution, the geometric standard deviation (sd_g) is the antilog of the standard deviation of the sample value logarithms, and 68.26% of all values lie between m_g/sd_g and $m_g \times sd_g$.
>
> If the short-term exposure values in a given situation have a geometric standard deviation of 2.0, 5% of all values will exceed 3.13 times the geometric mean. If a process displays variability greater than this, it is not under good control, and efforts should be made to restore control.”

US EPA (1992):

> “Exposure and dose profiles often fall in a skewed distribution that many times appears to be approximately lognormally distributed, although statistical tests for lognormality may fail. The arithmetic mean and the median are the same in a normal distribution, but exposure data are rarely normally distributed. As the typical skewness in the distribution increases, the exposure or dose distribution comes to resemble a lognormal curve where the arithmetic mean will be higher than the median. It is not unusual for the arithmetic mean to be located at the 75th percentile of the distribution or higher. Thus, the arithmetic mean is not necessarily a good indicator of the midpoint (median, 50th percentile) of a distribution.
>
> The average estimate, used to describe the arithmetic mean, can be approximated by using average values for all the factors making up the exposure or dose equation. It does not necessarily represent a particular individual on the distribution, but will fall within the range of the actual distribution.

Historically, this calculation has been referred to as the average case, but as with other *ad hoc* descriptors, definitions have varied widely in individual assessments.

When the data are highly skewed, it is sometimes instructive to approximate the median exposure or dose, or median estimate. This is usually done by calculating the geometric mean of the exposure or dose distribution, and historically this has often been referred to as the typical case, although again, definitions have varied widely. Both the average estimate and median estimate are measures of the central tendency of the exposure or dose distribution, but they must be clearly differentiated when presenting the results."

"Exposure assessments should take into account the time scale related to the biological response studied unless the assessment is intended to provide data on the range of biological responses (NRC, 1990, p. 28). For many noncancer effects, risk assessments consider the period of time over which the exposure occurred, and often, if there are no excursions in exposure that would lead to acute effects, average exposures or doses over the period of exposure are sufficient for the assessment. These averages are often in the form of average daily doses (ADDs). An ADD can be calculated from Equation 2-2 by averaging D_{pot} over body weight and an averaging time, provided the dosing pattern is known so the integral can be solved. It is unusual to have such data for human exposure and intake over extended periods of time, so some simplifying assumptions are commonly used. Using Equation 2-4 instead of 2-2 or 2-3 involves making steady-state assumptions about C and IR, but this makes the equation for ADD easier to solve. For intake processes, then, using Equation 2-4, this becomes:

$$ADD_{pot} = [\,\bar{C} \cdot \bar{IR} \cdot ED\,] \;/\; [BW \cdot AT]$$

Where ADD_{pot} is the average daily potential dose, BW is body weight, and AT is the time period over which the dose is averaged (converted to days). Concentration is best expressed as an estimate of the arithmetic mean regardless of the distribution of the data."

RISK CHARACTERIZATION

Temporal Matching of Toxicological Endpoint and Exposure Period

A key to credibility and meaningfulness of any risk assessment is the appropriate pairing of exposure duration with toxicity study duration or observed time to effect (Ross et al., 2001). The SF RCD is particularly weak in this area. The Haber Principle indicates that for many compounds, longer exposure results in lower NOAELs. This is not always true, however (Cochran and Ross, 2003), and it does not appear to be true for SF in particular. If one examines LOAEL for neurotoxicity (Table 15 of the RCD), it is remarkably stable over short to long durations of exposure. There appears to be several causes for the mismatches of exposure duration and toxicity study duration in the SF assessment. The primary cause appears to be policy differences between the Medical Toxicology Branch and the Worker Health and Safety Branch and perhaps a failure to communicate the need for chemical-specific exposure durations. This is alluded to in the RCD on page 55 "Since the exposure durations in the toxicology studies are defined differently than some of the scenarios in the Exposure Assessment (Appendix C), the applicable NOELs for the exposure durations are presented in Table 23." With the rapid dissipation rate of a gas, the exposure duration can have a dramatic effect on the absorbed dosage.

The example of short-term exposure is a particularly pertinent mismatch. Worker Health and Safety derived an estimate of short term exposure based on 1-7 days of exposure, while Medical Toxicology used an endpoint from the two-week rabbit inhalation study. Thus, while Worker Health and Safety provided a 95 percentile upper bound estimated exposure for one week of exposure, Medical Toxicology calculated MOE from a two-week duration rabbit toxicity study. The net effect is not significant for workers, but for residential exposures, the differences are large. For example, air levels reentering a treated structure fall to zero before day 7 and if exposure were averaged over 2 weeks rather than 1 week, MOEs would more than double and consistently exceed 100.

Another example of mismatch of exposure duration and toxicity study duration occurred in the interpretation of the acute neurotoxicity study in which rats were exposed 12 hours (2x6 hr) in a 30 hour period of time. Medical Toxicology calculated the dosage on a 24 hour basis (functionally lowering the NOEL by 22%). Worker Health and Safety derived a 95^{th} percentile estimate of exposure for 0-1 or 0-2 days. If exposure had been estimated at 0-1.25 days (i.e., the 30 hour duration of the toxicity study), and compared to the NOAEL over the same period of time, MOE would again consistently exceed 100. The lack of congruity between the toxicology study duration and human exposure duration suggests there may be poor communication between branches.

There is no subchronic, or chronic/lifetime exposure to residents from structural fumigation with Vikane for several reasons. First, structural fumigation is costly (typically ≥$2,000) and disruptive if the structure is inhabited because it displaces a family from their residence for several days. Secondly, homes are most frequently fumigated as a condition of real estate sale (they are uninhabited at the time fumigation is required). Thirdly, a re-infestation of dry wood termites requires approximately 4 years to achieve a "critical mass" when visible damage might be observed. Finally, the exposure estimates derived for these endpoints are not credible because they amortize 1-7 days of exposure over durations that are orders of magnitude larger. Given that many of the toxic effects experienced from acute or short term exposure to SF below the LOAEL are reversible, there is no carryover of effect from doses spaced years apart.

UNCERTAINTY

Using the 95th percentile for acute and short term exposure appears to be policy, but the scientific basis for the policy (which increases the acute and short term exposures approximately 4-fold over a central tendency value) appears to be neither stated nor referenced. The upper bound estimate of acute exposure is particularly onerous because it is purely theoretical. A structure might be inhabited immediately after it was cleared for occupancy, but this is an extremely rare occurrence. The practice of calculating an upper bound (with low probability) exposure on a low probability event is troubling. A resident is typically not allowed to reoccupy their homes for 12 hours after the structure is cleared i.e., the morning after it was cleared. Most of the fumigated houses were not occupied immediately prior to fumigation with little prospect of immediate occupancy after the fumigation because they were involved in a real estate transaction. Thus, DPR has calculated acute exposure on the basis of 3 concurrent low probability events. This practice goes beyond “health protective”, but that was not communicated to risk managers.

Because the RCD will be the basis of any subsequent risk mitigation, it is imperative that the risk manager be honestly apprised of the degree of conservatism inherent in this particular RCD. The RCD risk appraisal section provides some qualitative indications of the degree of conservatism, but makes no attempt to quantify it. There is a large amount of conservatism built into both the hazard identification/dose response (NOEL) portion as well as the exposure portion of the RCD on SF. Exposures tend to be overestimated and the NOELs tend to be underestimated, thus resulting in a multiplicative conservative bias far beyond the 100-fold uncertainty that is acknowledged.

On the hazard identification side, we have already discussed the bias in the interpretation of NOELs. In most instances, Dow AgroSciences agrees with the choice of study in characterizing hazard for that exposure duration, but disagrees with interpretation of the absorbed dose in that toxicity study. Dow AgroSciences frequently agrees with the concentration of SF chosen as NOEL, but does not agree on how that concentration is transformed into dosage. In most cases, CDPR appears to have erred on the conservative side, but there are exceptions. To briefly summarize, Dow AgroSciences believes that the acute toxicity endpoint NOEL from Albee et al., 1993 is underestimated by 22%. This is because CDPR is interpreting this study as though dosing was in 24 hour intervals, when in fact the exposure terminated at 30 hours, and neurotoxicity effects-testing began immediately thereafter. Thus the averaging time is 1.25 days and not 1 or 2 days. For the chronic endpoint (which should be based on the lifetime inhalation study in rats, and not the subchronic rat reproductive toxicity study), if the chronic study endpoint used was nephrotoxicity the NOEL would increase four-fold. Detailed explanations of these interpretive issues are provided in other parts of this document. The differences in estimation of NOAEL dosages between CDPR and Dow AgroSciences are summarized in the Table below.

Summary of Underestimated NOAELs Derived by CDPR for Vikane			
Variable	**CDPR**[a]	**Realistic**[b]	**Underestimate**[c]
Acute dosage	300 mg/kg/day	384 mg/kg/day	22%
Chronic dosage	4 mg/kg/day	16 mg/kg/day	4

[a] Dosages used in CDPR's final draft RCD assessment
[b] Dosages more consistent with the data
[c] Underestimate of dosage compared to CDPR's estimates (negative numbers signify overestimate)

On the exposure side, there are several quantifiable overestimates that have been used by CDPR. For the acute and short term exposures, it is not clear why CDPR used the 95th percentile exposures rather than an estimate of central tendency. Using the 95th percentile for acute and short term exposure appears to be policy, but the scientific basis for the policy (which increases the acute and short term exposures approximately 4-fold over a central tendency value) appears to be neither stated nor referenced. The upper bound estimate of acute exposure is particularly onerous because it is purely theoretical. A structure might be inhabited immediately after it was cleared for occupancy, but this is an extremely rare occurrence. The practice of calculating an upper bound (with low probability) exposure on a low probability event is troubling. A resident is typically not allowed to reoccupy their homes for 12 hours after the structure is cleared i.e., the morning after it was cleared. Most of the fumigated houses were not occupied immediately prior to fumigation with little prospect of immediate occupancy after the fumigation because they were involved in a real estate transaction. Thus, DPR has calculated acute exposure on the basis of 3 concurrent low probability events, i.e., the actual exposure calculated is closer to the 99.9th percentile. This practice goes beyond "health protective", but that was not communicated to risk managers. Additional overestimates (20-30%) occurred because the Florida-fumigated houses were excluded from estimates of residual air levels, although these homes had been cleared to the same levels as California houses. Further, the short term exposures are calculated for a maximum of 7 days and not for the duration of the 14-day rabbit toxicity study thereby overestimating exposure at least 2-fold. Additionally, CDPR has traditionally used a central tendency estimate for multi-day exposures and no reason was given for deviating from the method traditionally used (and the method used by other regulatory agencies throughout the world). Other obvious overestimates resulted from assuming a 40-year SF handler career, when 2 independent epidemiology studies cited in the RCD clearly indicated the average career span for SF handlers was 3-7 years (Anger, 1986; Calvert et al., 1998). The assumption that workers are involved in fumigation 52 weeks per year is very difficult to support. Whether due to sick leave, vacation, weather prohibitions, work activities not involving fumigation, or equipment shortages, it is extremely unlikely an employee will handle SF 52 weeks per year. Another significant overestimate is clearly visible from available data (Table 2 of HS-1834), and this has to do with commodity fumigation exposure. Commodity fumigation amounts to <0.1% of total SF usage and cannot occur more than a few times per year based on amount used. DPR should have access to both the number of use sites and average amount used per event, and it is doubtful that the estimated use frequency (5 days per week, 52 weeks per year) provided in the RCD agree with the estimates of commodity use shown in Table 2 of the RCD. Finally, the exposure frequency (number of days per week) was not used to calculate short or intermediate term worker exposure, although such a correction was used to calculating the animal NOEL. This results in approximately a 2-fold overestimation of exposure. A summary of the major discrepancies are summarized in the following Table.

Partial Summary of Conservative Factors Applied to Estimated Exposures Derived by CDPR for Vikane

Variable	**CDPR**[a]	**Realistic**[b]	**Overestimate**[c]
Resident Post Clear, acute	95^{th} percentile	mean	4
Resident Post Clear, subacute	7-day, 95^{th} %tile	14-day avg	>8
Resident Post Clear	Exclude FL data	Include FL	1.25
Resident/Bystander chronic	Annual fumigate	>10 yr cycle	>10
Commodity fumigate freq	5 d/wk, 52 wk/y	10 days/yr	26
Use frequency (days per week)	7/7 Short/Interm.	3.7/7 to 4/7	1.8 to 1.9
Body Weight (worker)	70 kg	85 kg	1.2
Vikane Handler freq	52 wk/yr	48 wk/yr	1.1
Vikane Handler duration	40 years	10	4

[a] Exposure defaults used in CDPR's final draft RCD assessment
[b] Exposure factors more consistent with "normal"
[c] Overestimate of exposure compared to Dow AgroSciences' estimates

CALCULATION OF MARGINS OF EXPOSURE (MOE)

The calculations of MOEs within the RCD include the questionable use and interpretation of the available sulfuryl fluoride toxicology and exposure data. In addition, unnecessarily conservative assumptions regarding the calculation of exposure, and in turn risk, are included in the RCD. To fully, and accurately use the information available to support the evaluation of sulfuryl fluoride, and to establish a more realistically conservative evaluation of human, inhalation risk for the various subpopulations that can encounter exposures to sulfuryl fluoride (Vikane), the following refined MOE are calculated and presented. For each subpopulation, the MOE (or range of MOEs) calculated within the RCD are refined by correcting misinterpretations of the data, or by substituting a more realistic data set or interpretation of the data These adjustments are described as “Adjustment Factors” (AF) and are described sequentially. Several other adjustments could be made (see Uncertainty section). The combination of the AFs for each of the subpopulations is utilized to calculate the final MOEs for the DWT scenarios. Although not summarized here, the same AF would be useful to recalculate human inhalation exposure potential in the PPB scenarios.

The range of the refined MOEs (450 to 70,890 for workers and 106 to 7,087 for residential subpopulations) using realistically conservative exposure assumptions and appropriate interpretations of the sulfuryl fluoride toxicological data all satisfy the minimum regulatory target of 100. The MOEs calculated and described within this document support the perspective of Vikane uses in the State of California as representing acceptable human inhalation exposure and risk potential when handled in conformance with product label directions and local regulations.

Occupational Exposure and Risk

Fumigator Worker (Total Activities) - Acute	
RCD Calculated MOE	**1,111**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Air concentration input for calculation (Highest “Shift-TWA” measured vs. 95th Percentile calculated)	AF = 1.08x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**3,107**

Tent Crew Workers (Total Activities) - Acute	
RCD Calculated MOE	**34**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Air concentration input for calculation (Highest “Shift-TWA” measured vs. 95th Percentile calculated)	AF = 19.9x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**1,752**

Fumigator Worker (Total Activities) – Short-Term	
RCD Calculated MOE	**308**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. 95th Percentile calculated)	AF = 56.5
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**42,913**

Tent Crew Workers (Total Activities) – Short-Term	
RCD Calculated MOE	**17**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. 95th Percentile calculated)	AF = 33.8x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**1,417**

Fumigator Worker (Total Activities) – Intermediate/Annual	
RCD Calculated MOE	**90**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 56.5
Worker frequency and duration assumption (work occurs for an individual 48 weeks rather than 52 weeks a year)	AF = 1.08x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**13,543**

Tent Crew Workers (Total Activities) – Intermediate/Annual	
RCD Calculated MOE	**5**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 33.8x
Worker frequency and duration assumption (work occurs for an individual 48 weeks rather than 52 weeks a year)	AF = 1.08x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**450**

Fumigator Worker (Total Activities) – Lifetime	
RCD Calculated MOE	**53**
Appropriate Chronic NOEL for systemic effects relevant to humans (20 ppm vs. 5 ppm in RCD)	AF = 4.0x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 56.5
Worker frequency and duration assumptions (work occurs 48 weeks for an individual rather than 52 weeks a year and nominal career length is 10 years for these workers rather than 40)	AF = 4.32x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**70,890**

Tent Crew Workers (Total Activities) – Lifetime	
RCD Calculated MOE	**3**
Appropriate Chronic NOEL for systemic effects relevant to humans (20 ppm vs. 5 ppm in RCD)	AF = 4.0x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 33.8x
Worker frequency and duration assumptions (work occurs 48 weeks for an individual rather than 52 weeks a year and nominal career length is 10 years for these workers rather than 40)	AF = 4.32x
Inappropriate correction of air monitoring results (an adjustment up from 66.1% was made in the RCD)	AF = 1.37x
Final, Adjusted MOE	**2,400**

Residential Exposure and Risk

Residential Re-Entry Exposure Following Clearance – Acute	
RCD Calculated MOE	**91 to 273**[1]
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Air concentration input for calculation (Dow AgroSciences calculated 95th percentile value of 1.13 ppm vs. RCD 95th percentile value of 1.78 ppm; HS-1834 Table 12)	AF = 1.57x
Final, Adjusted MOE	**270 to 810**

[1] The described range is derived from the calculated MOEs for the various age groups within this subpopulation

Residential Re-Entry Exposure Following Clearance – Short-Term[2]	
RCD Calculated MOE	**52 to 154**
Appropriate time-averaging factor (the NOEL was a 14 study which requires air concentrations to be amortized over 14 days rather than 7 days)	AF = 2.0x
Air concentration input for 7-day TWA calculation (Dow AgroSciences calculated 95th percentile value of 0.34 ppm vs. RCD 95th percentile value of 0.42 ppm; HS-1834 Table 12)	AF = 1.24x
Final, Adjusted MOE	**129 to 382**

[2] Although Dow AgroSciences does not believe that there are any exposure potentials for residential subpopulations (both residential re-entry and bystander) beyond 2 days following a fumigation (i.e. "acute"), adjusted "short-term" MOEs are calculated within this document to illustrate the refinements that should be made to those values that are calculated within the RCD.

Residential Bystander Exposure During Fumigation – Acute	
RCD Calculated MOE	**938 to 3750**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Final, Adjusted MOE	**1,773 to 7,087**

Residential Bystander Exposure During Aeration (TRAP) – Acute	
RCD Calculated MOE	**56 to 222**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Final, Adjusted MOE	**106 to 420**

Residential Bystander Exposure During Aeration (STACK) – Acute	
RCD Calculated MOE	**170 to 667**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Final, Adjusted MOE	**321 to 1,261**

dpr

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Acting Director

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M E M O R A N D U M

TO: Gary Patterson, Ph.D.
Supervising Toxicologist
Medical Toxicology Branch

VIA: Keith Pfeifer, Ph.D., D.A.B.T. [*original signed by Keith Pfeifer*]
Senior Toxicologist
Medical Toxicology Branch

FROM: Lori O. Lim, Ph.D., D.A.B.T. [*original signed by Lori Lim*]
Staff Toxicologist
(916) 324-3515

DATE: July 26, 2004

SUBJECT: RESPONSES TO COMMENTS FROM DOW AGROSCIENCES ON DRAFT SULFURYL FLUORIDE RISK CHARACTERIZATION DOCUMENT

This memorandum addresses toxicology and risk characterization related comments from Dow AgroSciences (DAS, SBRA 207653) on the draft Risk Characterization Document (RCD) (March 16, 2004). Some of the comments were the same as those submitted by DAS (March 18, 2004) for the Department's document dated February 23, 2004 and titled, "Identification of Definitive Toxicity/Exposure Studies and Critical Endpoints/NOELS for the Active Ingredient Sulfuryl Fluoride." In summary, the critical NOELs and endpoints used to determine the margins of exposure in the draft RCD do not need to be revised. Additional details to the toxicity studies and discussion of issues and rationale will be added to the revised RCD. Exposure specific comments are addressed by the Worker Health and Safety Branch.

I. Page 7 under Frequency and duration of exposure: "Calculation of short term", "intermediate term" and "annual" absorbed daily dose (ADD) values for residents should not be necessary given their infrequent and short duration exposures."

Response: The exposure durations in the RCD reflected potential human exposures based on the use pattern allowed on the label. However, margins of exposure, as risk estimates, were calculated only when there are toxicology studies of similar exposure duration or when weight of evidence indicates the NOELs were appropriate for use.

The following is a comparison of DAS proposed scenarios and those selected in the RCD for the risk calculation. There are two differences between scenarios DAS and DPR:

a. The duration defined by DAS and those in the RCD were different.
b. DPR did not estimate the risk of lifetime exposure for workers. Lifetime risk is calculated only when there is evidence of oncogenicity. Non-oncogenic effects due to repeated annual exposures were addressed by the NOEL for chronic annual exposure.

The use of this chronic NOEL would result in lower MOEs for lifetime exposure than for chronic exposure.

Scenarios	Acute	Short-term	Intermediate	Annual	Lifetime
DAS exposure scenarios					
Duration	1 to 2 days	up to 14 days	up to 13 weeks	up to a year	lifetime
Worker	Y	Y	Y	Y	**Y**
Resident (re-entry)	Y	NA	NA	NA	NA
Bystander	Y	NA	NA	NA	NA
Medical Toxicology risk calculation scenarios					
Duration	one day	1-7 days	1 week to <1 year	1 year	lifetime
Worker	Y	Y	Y	Y	**NA**
Resident	Y	NA	NA	NA	NA
Bystander	Y	NA	NA	NA	NA

II. Page 10 under Toxic Air Contaminant Consideration: DAS questioned, "whether air on a work site is ambient air, i.e., we do not believe this regulation applies to workers. Secondly, a specific ambient air concentration for regulatory purposes is not identified (there are several with varying durations of exposure and it is not clear which is defining criteria for AB 1807). Thirdly, air concentrations are not shown in Tables 17-22."

<u>Response</u>: First, DPR has used application site air concentration as the acute ambient air concentration for AB 1807 evaluation of pesticides; for example, methyl parathion and metam sodium. Regional air monitoring data are used for subchronic and chronic exposures. Second, the RCD clearly stated that the recommendation for listing was based on the reference concentrations, which were listed in Table 16. The Director has not made a determination for the air concentration for human protection; this step comes after AB 1807 Scientific Review Panel review and completion of the risk assessment process. Third, Tables 17-22 (in the March 2004 draft of RCD) cited where air concentrations are indicated in the Exposure Assessment (Appendix C).

III. Pages 10 to 17 under Epidemiology. DAS concluded that the two studies of methyl bromide and sulfuryl fluoride fumigation workers in California (Anger et al., 1986) and Florida (Calvert et al., 1998) did not demonstrate adverse health effects.

Page 10, "...the study (Anger et al., 1986) <u>does not</u> support the statement that sulfuryl fluoride has any effects on any of the endpoints examined, including cognitive." Similar statement is found on Page 14, last sentence.

Page 11, "...the current study (Calvert et al., 1988) does not show an adverse health effect due to long-term low level exposures to sulfuryl fluoride."

Page 15, last sentence, "...the results of the Calvert et al., (1998) study should be attributed to factors other than sulfuryl fluoride."

Page 17, third paragraph, "The results of Calvert et al. study of structural fumigant workers are better explained by bias, confounding or chance than exposure to fumigants...In light of the above mentioned weaknesses and inconsistencies, the current study (Calvert et al., 1988) does not show an adverse health effects due to long-term low level exposure to sulfuryl fluoride."

Response: The summaries of these two studies in the RCD reflected what was stated in the reports. As pointed out in both the RCD and DAS in their submitted comments, these studies had limitations and confounding factors. Therefore, definitive statement should not be made as to whether sulfuryl fluoride caused or did not caused the effects discussed in the papers.

IV. Page 17 under Selection and Treatment of Proper Acute NOEL. On top of Page 18, DAS stated that it, "...agrees with the selection of the ...endpoint as well as the NOEL of 300 ppm for this study...However, DPR calculated NOEL...significantly underestimates the relevant internal dose to the rats and thus underestimates the MOE for humans. The two-day acute study was specifically designed to evaluate neurotoxicological and points immediately following the second of two daily exposures..."

Page 19, last paragraph: "Since potential bystander exposures from fumigation and aeration occur within a 30-hr time period, the total exposure from the two-day acute neurotoxicity study is relevant..."

Response: DPR recognizes that the 2-day acute neurotoxicity study protocol (Albee *et al*., 1993a and b) was specifically designed to determine the toxicity following reentry and was approved by the U.S. EPA to meet the acute neurotoxicity study requirement. Since no effects were observed at 300 ppm, the highest dose tested, the U.S. EPA concluded that this exposure scenario was not of concern. At the same time, the U.S. EPA did not evaluate single day exposure because a toxicity endpoint from a single exposure was not available.

In comparison, DPR is concerned about acute exposures, especially to peak concentration, of workers and bystanders, and residents on the first day of reentry. It is unfortunate that the two-day study did not include any observations for the first day and the highest dose did not show any effects. Lacking the standard 1-day acute neurotoxicity study, DPR chose to use the results from this two-day study because it is more comprehensive than other acute studies. As explained in the RCD under the Risk Appraisal section (**V.B. HAZARD IDENTIFICATION**), this NOEL of 300 ppm when expressed in terms of dosage (300 mg/kg/day) is supported by data from other acute exposure studies. Lethargy was observed at 500 mg/kg/day (750 ppm after 4 hours) and death at 600 mg/kg/day (600 ppm after 6 hours between the 2nd and 6th dose) in rats (Table 3 in the RCD). These values are lower than the DAS proposed acute NOEL of 567 mg/kg/day extrapolated from the 300 ppm NOEL. Furthermore, the label does not restrict human exposure to 30-hours with 18-hours of no exposure between daily exposures as designed in this study. An adjusted NOEL using this fixed exposure scheme would have limited uses. Therefore, the critical acute NOEL should remain at 300 ppm or 300 mg/kg/day.

V. Page 19, second paragraph, "...The internal dose...actual average body weight of 0.1435 kg for the rats on the study and an inhalation rate of 0.1626 m^3/day..."

Response: The DAS breathing rate for rats used for the two-day acute neurotoxicity study (Albee *et al*., 1993a and b) is based on the U.S. EPA allometric equation (U.S. EPA, 1988) and is equivalent to 1.13 m^3/kg/day for a 0.1435 kg rat. This value is 15% higher than DPR's default value of 0.96 m^3/kg/day for all adult rats. Since actual breathing rate was not measured in any study and these values are of similar magnitude, the DPR default value should continued to be used for the conversion of sulfuryl fluoride air concentration to dosage in the RCD.

VI. In several places in the DAS document, the sulfuryl fluoride toxicity was attributed to fluoride.

Page 20, third paragraph, "The results of the pharmacokinetic study suggest that sulfuryl fluoride toxicity is the result of metabolic release of fluoride ions."

Page 23, first sentence, "...lack of systemic exposure to sulfuryl fluoride and indicates that the systemic toxicity of this fumigant is due to fluoride."

Page 24, third bullet and fourth paragraph: "...systemic toxicity elicited by sulfuryl fluoride is due to the release of fluoride ions, rather than a direct toxic action of sulfuryl fluoride."

Response: At the meeting with DAS representatives (June 15, 2004), DAS proposed that fluoride was released due to hydrolysis of sulfuryl fluoride in the mucus membrane of the nasal passage, and fluoride was responsible for all toxicological endpoints observed in the studies. When questioned by DPR, DAS indicated that they did not have any experimental data to support this proposal. They further indicated that they had not performed a comparison of toxicity between sulfuryl fluoride and fluoride since, in their opinion, the evidence for fluoride toxicity in the open-literature was inconclusive.

DPR is in agreement with DAS that fluoride was released in the metabolism of sulfuryl fluoride as detected in the pharmacokinetic study (Mendrala *et al*., 2002), and shown by dental fluorosis in repeated exposure studies. However, DPR is uncertain about the role of fluoride on other endpoints such as vacuolation in the brain, glomerulonephropathy, and lung inflammation observed in chronic exposures to relatively low concentrations of sulfuryl fluoride. These endpoints have not been found in published studies with fluoride alone. If fluoride is indeed involved, then these studies with sulfuryl fluoride provided the first evidence for fluoride-induced neurotoxicity. This has been a controversial issue. The only published study on this endpoint (Mullenix *et al*., 1995) was considered by the U.S. EPA as inconclusive (Baetcke *et al*., 2003). Until more conclusive evidence on the role of fluoride in non-dental endpoints, fluoride exposure is not considered in this risk assessment.

VII. Page 21 under Calculations from No-Observed Effect Levels (NOEL), DAS commented that the RCD was inconsistent in normalizing animal exposure vs. human exposure...If normalization is needed in the conversion of animal NOELs to human NOELs for short term, subchronic and chronic potential exposures then the two terms used in the conversion of the NOELs must be accounted for in the calculation of exposure estimates."

Response: Since the exposures in the toxicity studies and those for humans are usually not the same, there is no accurate method to match the duration of these exposures. In the RCD, the NOELs as ppm air concentration were amortized to daily exposure dosage (mg/kg/day) for all exposure durations. As discussed in response to other comments, there is uncertainty related to this approach, which may result in the over- or under-estimation of the risk depending on the exposure scenario. DPR will review any additional toxicology studies, which may better characterize the risk.

VIII. Page 22 under Calculation of Reference Concentration, DAS commented that "...the calculation of the reference concentration using a child-specific respiration rate is not applicable to durations of exposure that do not exist for the child..."

Response: The revised RCD will provide RfCs for both children and adults. The child RfC is applicable for all residential and bystander exposure scenarios while the adult RfC is applicable only for occupational exposure.

IX. Page 22 under Mammalian Pharmacokinetics and Metabolism (ADME), DAS commented that DAS, "...recently has completed and submitted to DPR an inhalation pharmacokinetic study by Mendrala et al., 2002."

Response: This cited study (Mendrala *et al*., 2002) was received by DPR on February 22, 2004. The MT did not review this study until the draft RCD was completed. It would have been helpful if DAS had submitted this 2002 study earlier.

X. Page 24, first paragraph, "An absorbed dose was estimated on measured internal dose from radioactivity as compared to internal dose estimated from inhalation rate and body weight. The estimated absorbed dose was 14.1% or 12.4%, respectively, for exposure concentrations of 30 ppm and 300 ppm. However, internal dose calculations for purposes of risk assessment were based on the default of 100% absorption."

Response: In the RCD, a default 100% absorption factor was used because the pharmacokinetic study was not available (see **Comment IX**). Based on results from this study and using the same equation as DAS but with the DPR rat default breathing rate, the DPR calculated absorption factors are 18% and 16%, for 30 ppm and 300 ppm, respectively (see **Comment IX**). There are uncertainties associated with these values since actual breathing rates were not measured in the study, and there are anatomical differences in the respiratory tract of rats and humans. DPR will be revised the exposures using 18% as the absorption factor. In should be noted that the MOE calculations are not affected by the magnitude of this factor because the same absorption factor is applied to both the NOEL and the exposure with the assumption that the absorption for the rats is the same as humans.

XI. Page 24-25 under Dose Calculation based on 2-Generation Rat Reproduction Study, DAS commented that "...Risk Assessments must take into consideration that the rats on the reproduction study actually were exposed for 6 hours/day, 7 days/week during mating, gestation, and lactation through two generations."

Response: The RCD stated only one exposure regimen (5 days/week) and will be revised to include more details for this study (Breslin *et al*., 1992). The protocol as described in the report is indicated in the following table. As shown in the table below, the rats were exposed 5 days/week during premating (for 10 weeks for F0 and 12 weeks for F1, excluding holidays), and 7 days/week during mating (1 to 3 weeks), gestation (3 weeks), and lactation (3 weeks). The exposure during gestation and lactation (to postpartum day 21) was not continuous because females were not exposed to sulfuryl fluoride from gestation day 21 to postpartum day 4 (about 10 days). For the F0 generation, the total duration was about 20 weeks and approximated a subchronic exposure-type scenario. For the F1 generation, the total duration was longer with *in utero*, lactation, premating, mating, gestation, and lactation periods of exposures. While the total was about 25 to 27 weeks, it is not appropriate to simply add up the weeks of exposure for the F1 generation. These periods of exposures for this generation expand from fetus to adulthood with days of no exposures in between. Therefore, the F1 exposure should be considered a chronic exposure scenario.

Week	**F0**	**F1**
1-10	Premating at 6 weeks old Exposed 6 hrs/day, 5 days/week (excluding holidays)	
11	Mating/gestation/lactation Exposed 6 hrs/day, 7 days/week, to postpartum day 21, except no exposure for females from gestation day 21 to postpartum day 4. Exposure during mating was 1 to 3 weeks.	
12		
13		
14		Fetus/Pup exposure: -In utero up to gestation day 20 to birth -Via milk from birth to postpartum day 21. -No exposure from 3 to 6 weeks old (after weaning)
15		
16		
17		
18		
19		
20-31	Sacrifice on week 20	Premating (assume at 6 weeks old) Exposed 6 hrs/day, 5 days/week (excluding holidays)
32-41		Mating/gestation/lactation Exposed 6 hrs/day, 7 days/week, to postpartum day 21, except no exposure for females from gestation day 21 to postpartum day 4. Exposure during mating was 1 to 3 weeks.

As for the calculation of a daily dosage, DPR calculated the dosage (4 mg/kg/day) for the NOEL (5 ppm) based on the continuous exposure period, which was during premating at 5 days per week. This approach also took into consideration days of no exposure during the periods of 7 days per week of exposure. In comparison, the dosage calculation performed by DAS assumed that the effects observed were due to repeated daily exposure during the entire study. Since daily exposure occurred only during parts of the study, this assumption results in an overestimation of the NOEL (6 mg/kg/day). Therefore, calculated dosage of 4 mg/kg/day for this study in the draft RCD remained the more appropriate value.

XII. Page 25 under Chronic NOEL Selection and Effects, second paragraph, DAS commented that, "a chronic NOEL (5 ppm) ...do not accurately reflect the effects of chronic exposure to SF. The increase in alveolar macrophages is a manifestation of the irritancy properties of sulfuryl fluoride to the respiratory tract which is a portal of entry effect rather than a systemic effect. In contrast to the increase in alveolar macrophages in the lungs of rats exposed to 20 ppm for 7 days/week for 4-5 months on the reproduction study, lungs of rats, mice or dogs exposed to 20 ppm sulfuryl fluoride 5 days/week for 12, 18 or 24 months did not have alveolar histiocytosis or other effects."

Response: There are three issues raised with this comment: (1) use of portal of entry effect and systemic effect for risk characterization, (2) exposures between 5 days/week and 7 days/week, and (3) comparison of NOEL based on air concentrations.

The DAS comment implied that irritation should not be used as a critical endpoint for risk characterization. At the meeting with DPR (June 15, 2004), DAS indicated that the irritation occurred at the nasal passages and was due to fluoride ions. DPR disagrees with the DAS position. First, pulmonary irritation should be considered an adverse effect because it can have severe consequences for people with certain health conditions such as asthma. Second, the lung effects reflected tissue injury and may not be due to nasal irritation alone. The data from the two-generation reproductive toxicity study (Breslin *et al*., 1992) showed that alveolar macrophage aggregates were found beyond the nasal passages in the subpleural and peribronchial locations. These lesions were frequently accompanied by chronic inflammation in the high dose group. As noted in the following paragraph from the study (pages 24-25 of the study report), the effects were considered evidence of lung injury by the study authors:

"The pathogenesis of spontaneously occurring aggregates of alveolar macrophages is unknown, but the incidence increases with age in untreated rats (Anver and Cohen, 1979) and was observed in control rats in this study. However, a common response to lung injury is an increase in these macrophages. With significant, repeated injury, multifocal lesions of the alveolar wall, with inflammatory cells, type II pneumocytes and alveolar fibrosis may be seen in addition to the luminal macrophages (Haschek and Witschi, 1991). This was the pathologic picture observed in many of the rats exposed to 150 ppm in which observations of "aggregates of alveolar macrophages" and "inflammation, chronic" were made."

The second part of the comment implied that the effect was due to continuous daily exposure (in the rat reproductive toxicity study) and pulmonary effects were not observed when animals were observed for 5 days per week exposure. As noted in the response to **Comment XI**, the dosing regimen in the reproductive toxicity study included both 5 days per week and 7 days per week regimen, plus some non-exposure days.

Third, DPR disagrees with DAS approach of comparing NOELs based only on air concentration. As with any chemical, there must be a mechanism for uptake in order for internal exposure to occur. DPR adjusts the NOELs with animal breathing rates to account for differences in the uptake between experimental animals. As shown in Table 13 of the RCD, lung inflammation and alveolar macrophage aggregates were observed in dogs with a similar NOEL in terms of dosage (6 mg/kg/day) (Quast *et al*., 1993) as that for the rat reproductive toxicity study (4 mg/kg/day).

XIII. Page 26, 2nd and 3rd Paragraphs,

"Dental fluorosis of rodent incisor teeth is an inappropriate model for humans since rat incisor teeth continue to grow throughout adult life."

"Humans are not susceptible to dental fluorosis after 6-8 years of age...Therefore, dental fluorosis is not a realistic possibility as a result of occasional, transient, low-level inhalation exposures to sulfuryl fluoride."

Response: With regard to dental fluorosis, the RCD did not base the risk estimation on this endpoint because other endpoints had lower NOELs. Dental fluorosis was not reported for acute exposure. Brain lesion was the most sensitive endpoint for 1-2 weeks, and subchronic exposures. The draft RCD clearly stated that the risk assessment considered respiratory system effects as the critical effect for chronic inhalation exposure. This statement was quoted in the first paragraph under the heading of **Chronic NOEL Selection and Effects** in DAS comments.

XIV. Page 28 under Evaluation of Neurotoxicity Endpoints, DAS commented that the "information on chlorfenapyr, spongiform encephalopathies and vacuolated neurons in aged rats is interesting, but is not relevant to sulfuryl fluoride. This inferential speculation should not be included or considered within the DPR assessment."

Response: This was a general discussion on vacuolation as an endpoint. The beginning of the paragraph clearly stated that the cause was unknown. The inclusion of other information served to show that vacuolation is not a rare event associated with sulfuryl fluoride exposure alone.

XV. Page 28, second paragraph, "In the comments on the long term and functional consequence of sulfuryl fluoride neurotoxicity, the RCD should include the findings and perspective provided by the evaluation of the recovery animals after 13 weeks of exposure as described in the report by Mattsson et al., 1986.

Response: This finding was already included in the RCD but citation will be added.

XVI. Page 29 under Respiratory Effects, DAS commented that pulmonary effects found in postmortem examinations of humans exposed to high sulfuryl fluoride concentration was not relevant to low level exposures, and should not used for weight-of-evidence.

Response: The revised RCD will add that the examinations were from human exposure at high concentrations (Scheurman, 1985), and lower concentrations since the house was cleared for entry (Dammann *et al*., 1987). DPR believes that findings from these studies are relevant since the lung is a target organ in experimental animal studies.

XVII. Page 30 under Aggregate Exposure Assessment, DAS questioned, "...CDPR's legislative and regulatory authority to discuss or plan to conduct risk assessments on

sources of fluoride that are non-pesticidal in origin. In so much as Dow AgroSciences has no control over pesticidal sources that it does not register (such as cyrolite), natural sources of fluoride, or exposure to fluoride from dental hygiene uses including additions to drinking water, we find CDPR's statement regarding cumulative toxicity of fluoride-generating compounds inappropriate in this pesticidal-specific risk assessment."

Response: DPR's legislative mandate is to conduct risk assessment for pesticides used in California. Aggregate exposure assessment is part of the risk assessment process and has been performed for many pesticides, including methyl bromide, another fumigant. It should be noted that the U.S. EPA included fluoride exposure from all sources in their evaluation of food uses of sulfuryl fluoride.

XVIII. Page 38 under Temporal Matching of Toxicological Endpoint and Exposure Period, DAS commented that there was mismatch between the NOELs and exposure durations, and suggested there was a failure of communication between MT and WHS Branches.

Response: The mismatch characterize by DAS is due to the lack of toxicity studies with protocols which match the exposure duration of concern. This disparity is common in risk assessment and the weight of evidence is necessary to determine the most reasonable match. The potential overestimation and underestimation of risks were discussed in the Risk Appraisal section of the RCD.

In the draft RCD, a two-week amortized NOEL (40 mg/kg/day for 100 ppm at 6 hours/day, 5 days/week; Eisenbrandt *et al*., 1985) was used to address any exposure of 1 to 13 weeks. The specific scenarios were: a. Fumigator and tent crew: 3.67- 4 days/week from 1 week to < 1 year based on mean exposure values, b. Resident after clearance for reentry: 1-7 days during reoccupation, and c. Handler in non-food commodity fumigation: 5 days/week for 1 week to <1 year. In the revised RCD, the risks for scenarios b and c have been eliminated.

DAS argued that the 2-week NOEL should not be amortized since human exposures were also 5 days per week. This is a reasonable argument if the label specifically limited the exposure to 5 days per week, or to one or two week intervals. In practice, workers are more likely to be exposed for several consecutive weeks during the year. Amortization is a means to reflect a lower potential NOEL due to <u>repeated</u> weekly exposures. While it may overestimate the risk associated with one or two week's exposure, it actually underestimates the risk for repeated weekly exposures, up to 13 weeks. For 13 weeks of exposure, the MOE was calculated using a subchronic NOEL of 12 mg/kg/day (3.5-fold lower than the 2-week NOEL). Therefore, there is no change to the 1-2 week NOEL but additional discussion will be provided to clarify why amortization was needed.

XIX. Page 40, last paragraph, DAS commented that the chronic toxicity endpoint should be based on nephrotoxicity.

<u>Response</u>: DPR disagrees with the selection of this endpoint and NOEL. See response to **Comment XII** about the relevancy of the respiratory endpoint.

cc. Jay Schreider
Joyce Gee
Peter Leung

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FROM: Donna DiPaolo, Ph.D. *(original signed by D. DiPaolo)*
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916-445-4262

DATE: July 27, 2004

SUBJECT: RESPONSE TO COMMENTS FROM DOW AGROSCIENCES LLC ON DRAFT SULFURYL FLUORIDE RISK CHARACTERIZATION DOCUMENT

This memorandum addresses comments directed to the exposure assessment sections of the Sulfuryl Fluoride Risk Characterization Document (RCD; March 16, 2004) electronically submitted by the registrant, Dow AgroSciences LLC (DAS), dated July 12, 2004. These comments have been considered and the Worker Health and Safety Branch response is provided below. The RCD main text and Appendix C (Exposure Assessment) have been revised when applicable.

Executive Summary comments (pages 3-4):

Comment 1:
Characterization of 10x "maximal" use rate at 10 times the initial concentration is incorrect. Information is provided to clarify that the 10x target is achieved by a combination of increased dose x increased holding time.

Response 1:
DPR has provided submaximal exposures to workers and bystanders based on registrant data collected during structural fumigations at termite application rates (~24 hour "holding" periods). The currently registered Vikane label states a 10x dosage factor, as a multiple of drywood termite dosage, for powder post and death watch beetles. It is DPR's practice to assess pesticide exposure based on the maximal label application rate and not typical use. Since no data were collected during maximal application rates (i.e., control of powder post beetles at 10x termite dosage), DPR multiplied exposures by 10-15 depending on the study application rates in comparison to that which would be used, according to the label, for powder post beetles under the same conditions. While applicators may decrease the amount of sulfuryl fluoride introduced by lengthening the holding period as presented by the registrant, the label does not place such restrictions or limitations on the maximal application rate.

Also, while DAS has provided tables with typical use rates, holding times, and terminal sulfuryl fluoride concentrations (page 6) comparing powder post beetle and termite applications, they have not provided data to support these values, and again these are typical values and not maximal values. Therefore, the exposure assessment (Appendix C) will not be changed to reflect typical use rates as requested by DAS. However, label language which restricts use to the typical rates may be considered during the mitigation process.

Comment 2:
Acute residential exposure was overestimated by 25% to several-fold depending on the scenario due to elimination of pertinent data and unsupported assumptions about reentry time relative to clearance. The rat absorbed dose for the acute toxicity NOAEL concentration was underestimated by 22% in the RCD due to inappropriate interpretation of study duration. Resulting acute MOEs were significantly underestimated.

Response 2:
Acute (first 24 hrs), short-term (1-7 days), annual, and lifetime exposures of residents reentering treated structures have been estimated to assess potential risk according to the label use of sulfuryl fluoride. The label does not restrict the number of fumigations to a structure, and sulfuryl fluoride treatment of a structure does not prevent pest reinfestation. Since DPR does not assess risk based on typical use (as surveyed by DAS), it is appropriate to estimate risks for these potential exposures durations. These exposure duration would be similar for bystanders (i.e., individuals living near a structural fumigation).

Regarding the dissipation of sulfuryl fluoride from a structure following fumigation and clearance according to the label and currently approved practices in California, the exposure assessment (Appendix C) estimated upperbound (Table 12) and mean (Table 11) indoor air concentrations based on the registrant's data collected from 7 California homes (Shurdut, 1995; Table 9 of Appendix C). As stated in Appendix C (page 20), WHS estimates the highest potential short-term exposure using a 95th percentile. While this may be a conservative estimate, it is necessary for DPR to attempt to protect those individuals who may be exposed above an average level.

The dissipation data submitted by the registrant (Shurdut, 1995) covered a 48-hour period following clearance (Table 9 of Appendix C) and indicated detectable levels of sulfuryl fluoride through this time. However, the registrant states on page 7 of their comments: "Actual measurements show that SF air concentrations are often below the limit of detection after 2 days." This statement implies that there are times, albeit not "often," that levels are detectable after 2 days. DPR respectfully submits that the modeling used to predict dissipation of sulfuryl fluoride (Table 10; Figures 4 and 5) is appropriate in assessing residential reentry short-term (1-7 days) exposure given the currently available data.

While the registrant submitted sulfuryl fluoride dissipation data from Florida homes, these homes were not used in the present exposure assessment since their aeration methods, as well as environmental conditions and housing composition may differ from California. If there are no differences between the dissipation data from the 2 states as the registrants states on page 31 of their response, then inclusion or exclusion of this data should not impact the present assessment. In addition, the registrant has indicated that they are developing a new aeration practice (i.e., Stack method) with the fumigation industry. Therefore, reevaluation of indoor air levels will need to be considered at that time since any change in aeration techniques and duration will impact residential reentry levels.

Comment 3:
Potential short term exposure was greatly overestimated because it was averaged over 7 days and not the 14-day duration of the toxicology study. The net result was a significant underestimation of short-term MOE.

Response 3:
The short term exposures were presented as daily absorbed dosages based on anticipated duration and frequency of exposure. These dosages were not averaged over 7 days. Refer to response by Medical Toxicology Branch regarding the selection of the appropriate toxicological data to determine MOE's.

Comment 4:
There is no subchronic (90 day) duration exposure to residents or bystanders, although it was calculated. This is because Vikane fumigation is a relatively rare event in neighborhoods, and the duration of exposure can be measured in hours not days, weeks, or months.

Response 4:
There were no intermediate-term (subchronic) exposures estimated for residents (Table 13) or bystanders (Tables 14-17). A change has been made to exposures of bystanders to nonfood commodity fumigation facilities; only acute, annual and lifetime exposures have been estimated based on the infrequent use of sulfuryl fluoride for nonfood commodity use, as indicated in the California Pesticide Use Report Database (DPR, 2004).

Comment 5:
Chronic exposures were estimated for residents and bystanders assuming annual fumigation of their homes, a situation that does not occur. Also, handlers were assumed to work 52 weeks of every year for 40 years. The net effect was a gross underestimation of chronic MOE.

Response 5:
Since there is no limitation to the frequency of structural fumigation on the current label, DPR appropriately assessed potential exposure to residents and bystanders as once per year, every year. While annual and lifetime exposures were estimated for residents and bystanders to structural fumigations in the exposure assessment (Appendix C), no risk was estimated based on the toxicologic data (Tables in IV.C. of RCD main text).

Comment 6:
The short-term and intermediate-term exposures were not amortized to reflect actual frequency of use by workers resulting in underestimation of margins of exposure by approximately 2-fold.

Response 6:
Short-term and intermediate-term exposures (daily absorbed dosages) considered numbers of hours per day involved in a given activity during which exposure may occur (Table 5 of Appendix C [Exposure Assessment]). Annual and lifetime exposures were amortized depending on the number of days per week a given activity may be performed. Refer to the response from Medical Toxicology regarding amortizing NOELs in light of potential human exposure duration/frequency.

Comment 7:
The chronic toxicity endpoint was, in fact, derived from a subchronic-duration rat reproductive toxicity study despite the existence of an acceptable chronic study. The rat exposure regimen in the reproductive toxicity study was 7 days per week for 70% of the duration, unlike the design of all the other intermediate to long-term studies. Had the chronic toxicity NOAEL been derived from the CDPR-accepted chronic study for a true adverse effect, it would be 4-fold greater.

Response 7:
See response by Medical Toxicology.

Comment 8:
The range of the refined MOEs (450 to 70,890 for workers and 106 to 7,087 for residential subpopulations) using realistically conservative exposure assumptions and appropriate interpretations of the SF toxicological data all satisfy the minimum regulatory target of 100. The MOEs calculated and described within this document support the perspective of Vikane uses in the State of California as representing acceptable human inhalation exposure and risk potential when handled in conformance with product label directions and state regulations.

Response 8:
Regarding exposure, maximal use allowed by the label directions were used to estimate exposure with upperbound levels used for short-term and mean values for longer-term (> 7 days). This level of protection is used in all exposure assessments and is clearly stated on page 20 of Appendix C (HS-1834). Typical application rates and frequency of exposures, as presented by the registrant, may be set as limits during the mitigation process to achieve MOEs $\geq$ 100.

Other comments (pages 5-42):

a) Pages 8-9, Nonfood commodity fumigation frequency survey.

Response:
Nonfood commodity worker exposure (Table 7a) and nonfood commodity bystander exposure (Table 17) have been adjusted to consider the infrequent use of sulfuryl fluoride in California (Table 2; DPR, 2004).

However, while the current use of sulfuryl fluoride in nonfood commodity fumigation may be rare in California, the currently approved Vikane label allows such use with no limitations or restrictions. If, in the future, nonfood commodity use of sulfuryl fluoride increases in California due to changes in fumigation practices or fumigant product availability (i.e., shift in methyl bromide or phosphine uses), the exposure of workers and nonworkers will need to be reassessed. Also, exposures resulting from food commodity use, as proposed on the pending ProFume product label, is not assessed in the present risk characterization of sulfuryl fluoride. Potential worker and nonworker exposures should be assessed prior to approval of registration in California.

b) Pages 9, Structural worker exposure duration and frequency.

Response:
Sulfuryl fluoride is used in California all year long (Figure 3 of Appendix C). According to a survey conducted by the United States Department of Labor, the average number of paid vacation days and holidays for blue-collar workers is 7.2 and 8 days, respectively (U.S. Department of Labor, 2004). Therefore, the present exposure assessment has been changed to consider an annual exposure duration of 49 weeks/year (15 days = 3 work weeks/year) rather than 52 weeks/year (Table 5). While the average time employed in the fumigation industry is undoubtedly less than 40 years, DPR uses this value to assess maximum potential risk. This is especially important when there is a risk from chronic exposure. Reducing or restricting a worker's exposure duration may be considered during the mitigation process.

c) Pages 10, Toxic air contaminant considerations.

Response:
Tables in IV.B. of the RCD main text refers to Tables 7-17 of Appendix C in which the air concentrations used to estimate absorbed dose are stated in the footnotes to each table.

Refer to Medical Toxicology's response regarding hazard identification/reference concentration.

d) Pages 10-17, Epidemiology.

Response:
Refer to response by Medical Toxicology.

e) Pages 17-22, Selection and treatment of proper acute NOEL and Calculations from NOELs.

Response:
Refer to response by Medical Toxicology.

f) Pages 22-24, Mammalian pharmacokinetics and metabolism.

Response.
Refer to the response by Medical Toxicology. The Exposure Assessment (Appendix C) will be revised to reflect the Medical Toxicology interpretation of the registrant's recently submitted study (Mendrala *et al*., 2002) in the pharmacokinetics section. Following concurrence by Medical Toxicology and Worker Health and Safety, the estimated inhalation absorption factor of 18% has been incorporated into the RCD.

g) Pages 24-29.

Response:
Refer to response by Medical Toxicology.

h) Pages 30-37, Exposure Assessment

Response:
Aggregate exposures (RCD, V.E.2-3) will be addressed by Medical Toxicology.

Regarding the correction for sample recovery in Contardi and Lambesis (1996):

> After review of the field spike recovery analysis by Contardi and Lambesis in light of the Huff and Murphy revalidation (1995), field spike recoveries were reevaluated in the present exposure assessment. Appendix I of the exposure assessment (Appendix C of the RCD) presents average recoveries for phases 2 and 3 of the worker study. Since recoveries were greater than 90%, the present exposure assessment was revised to use field sample data without adjustment for recovery (pages 23-24 of the present Exposure Assessment, Appendix C of RCD).

Regarding correction of the indoor air monitoring data reported by Shurdut (1995):

> In the Shurdut report, samples taken inside California homes were corrected by 64.3% (90.6% and 71%), while the present exposure assessment corrected samples by 64.6% based

on California recovery data (see Tables A-2 and A-3 of RCD, Appendix C). Data collected in California is preferable in estimating exposure, not only due to differences in aeration procedures, but also due to potential differences in home construction and meteorologic conditions between California and Florida. Although Model 2 accounted for most of the variance between the monitored homes, Model 1 was used to predict indoor air concentrations for houses not yet observed and differences between homes was treated as noise in the model when predicting concentrations in future homes.

Regarding the use of upperbound levels (page 35):

Since residential exposure was predicted to last for 7 days, and upperbound air concentrations (Figure 5, Table 12) were used in estimating short-term exposures (Table 13, acute and short-term ADDs). Since an individual may be exposed to this upperbound level in any one year, it was appropriate to estimate annual exposure was based on this upperbound level since the exposure is 7 days/year. The residential short-term exposures were weighted as area under the curve of Figure 5 for either 24 hours (acute ADD) or 7 days (short-term ADD). Residential exposures also considered the time persons were at home according to Table 8. (It should be noted that upper confidence limits were not used in the present exposure assessment.)

Regarding selection of proper indicator for central tendency:

DPR uses the arithmetic mean. The arithmetic mean is used rather than the geometric mean or the median because, although it can be argued that the latter statistics better indicate the location of the center of a skewed distribution, it is not the center that is of interest in exposure assessment, but the *expected magnitude* of the long-term exposure. While extremely high daily exposures are low-probability events, they do occur, and the arithmetic mean appropriately gives them weight in proportion to their probability. In contrast, the geometric mean gives decreasing weight as the value of the exposure increases, and the median gives no weight whatsoever to extreme exposures. (Refer to Powell, 2003 for further discussion of use of the arithmetic mean.)

i) Pages 40-42: Uncertainty.

<u>Response</u>:

As stated on page 20 of the exposure assessment (Appendix C): For short-term exposures (i.e., those with durations of 7 days or less) the WHS estimates the highest exposure an individual may realistically experience as a result of a label-prescribed activity. In order to estimate this “upper-bound” daily exposure, WHS generally uses the estimated population 95th percentile of daily exposure. A population estimate is used instead of a sample statistic because sample maxima and upper-end percentiles, in samples of the sizes usually available to exposure assessors, are both statistically unstable and known to underestimate the population values. The population estimate, on the other hand, is more stable because it is based on all the observations rather than a single value; moreover, it is adjusted, in effect, for sample size, correcting some of the underestimation bias due to small samples. A high percentile is estimated, rather than the maximum itself, because in theory, the maximum value of a lognormal population is infinitely large. In practice, exposures must be bounded because a finite amount of active ingredient is applied. The use of a high percentile acknowledges that the assumed lognormal distribution is probably not a perfect description of the population of exposures, especially at the upper extremes. The population 95th percentile is estimated, rather than a higher percentile, because the higher the percentile the less reliably it can be estimated.

References

Contardi, J. and Lambesis, D. 1996. Amended report for evaluation of sulfuryl fluoride exposure to workers during structural fumigations when using Vikane Gas Fumigant. DOW DECO-HEH2.1-1-182(131). Midland, Michigan: Industrial Hygiene Research and Technology, Health and Environmental Sciences, Dow Chemical Company. (DPR Doc. No. 50223-041, Report No. 148847).

DPR. 2004. California Pesticide Information Portal (CalPIP). Version 8.20. Queried for year (1998-2002); product (Vikane, Vikane fumigant, Vikane gas fumigant, sulfuryl fluoride); and chemical (sulfuryl fluoride), May 17, 2004 by Donna DiPaolo, Worker Health and Safety Branch, California Department of Pesticide Regulation. http://calpip.cdpr.ca.gov/cfdocs/calpip/prod/main.cfm

Huff, D. and Murphy, P. 1995. Sulfuryl Fluoride: Re-validation of air monitoring method HEH2.12-38-26(6). Midland, Michigan: Analytical Chemistry Laboratory, Health and Environmental Sciences, Dow Chemical Company. (DPR Doc. No. 50223-040, Record No. 145235).

Mendrala, A.L., Markham, D.A., Clark, A.J., Krieger, S.M., Houtman, C.E., and Rick, D.L. 2002. Sulfuryl fluoride: Pharmacokinetics and metabolism in Fischer 344 rats. Indianapolis, IN: Dow Agrosciences LLC. (DPR Doc. No. 50223-0067, Record No. 210013)

Powell, S. 2003. Why Worker Health and Safety Branch uses arithmetic means in exposure assessments. HSM-03022. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency.

Shurdut, B. 1995. Amended report for evaluation of concentration of sulfuryl fluoride inside houses following fumigation with Vikane Gas Fumigant. Indianapolis, Indiana: Global Human Exposure Assessment, DowElanco. (DPR Doc. No. 50223-039, Record No. 141960).

U.S. Department of Labor. 2004. National compensation survey: Employee benefits in private industry in the United States, March 2003. Summary 04-02. Washington, DC: Bureau of Labor Statistics, United States Department of Labor.

Responses to Comments on the August 2004 Draft

1. **Dow AgroSciences**
2. **Xtermite**

Dow AgroSciences Response

to

Sulfuryl Fluoride (Vikane*)

Risk Characterization Document

Draft

California Department of Pesticide Regulation

Dated August 26, 2004

by

Dow AgroSciences LLC

October 15, 2004

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Risk managers must rely on the Risk Characterization Document (RCD) to make decisions about the regulatory disposition of sulfuryl fluoride (SF), which is currently marketed as Vikane™ gas fumigant. It is imperative that the RCD present the toxicology and exposure information in both a scientifically credible and understandable manner. Because risk assessment involves interpretation of data, it is important that the path from data to interpretation and the scientific basis underlying the interpretations be transparent. Dow AgroSciences' review of the Vikane draft RCD revealed a number of incongruities that obscure the correct interpretation of the toxicology database for SF and the appropriate application of these data for purposes of quantitative exposure and risk analysis. The areas that had the most significant impact were misinterpretation or misunderstanding of the acute neurotoxicology study design and mismatching toxicology study duration with human SF exposure duration. These particular areas are critical because the appropriate interpretation of the toxicology data reveals that MOEs exceed 100 when appropriate durations and associated exposure scenarios are relied upon. The most important errors are summarized as follows:

1) Characterization of 10x "maximal" use rate at 10 times the initial concentration is incorrect. Information is provided to clarify that the 10x target is achieved by a combination of increased dose x increased holding time.
2) Acute residential exposure was overestimated by 25% to several-fold depending on the scenario due to elimination of pertinent data and unsupported assumptions about reentry time relative to clearance. The rat absorbed dose for the acute toxicity NOAEL concentration was underestimated by 22% in the RCD due to inappropriate interpretation of study duration. Resulting acute MOEs were significantly underestimated.
3) Potential short term exposure was greatly overestimated because it was averaged over 7 days and not the 14-day duration of the toxicology study. The net result was a significant underestimation of short-term MOE.
4) There is no subchronic (90 day) duration exposure to residents or bystanders, although it was calculated. This is because Vikane fumigation is a relatively rare event in neighborhoods, and the duration of exposure can be measured in hours not days, weeks, or months.
5) Chronic exposures were estimated for residents and bystanders assuming annual fumigation of their homes, a situation that does not occur. Also, handlers were assumed to work every year for 40 years. The net effect was a gross underestimation of chronic MOE.
6) The short-term and intermediate-term exposures were not amortized to reflect actual frequency of use by workers resulting in underestimation of margins of exposure by approximately 2-fold.
7) The chronic toxicity endpoint was, in fact, derived from a subchronic-duration rat reproductive toxicity study despite the existence of an acceptable chronic study. The rat exposure regimen in the

reproductive toxicity study was 7 days per week for 70% of the duration, unlike the design of all the other intermediate to long-term studies. Had the chronic toxicity NOAEL been derived from the CDPR-accepted chronic study for a true adverse effect, it would be 4-fold greater.

8) The range of the refined MOEs (245 to 2,807 for workers and 357 to 15,161 for residential subpopulations) using realistically conservative exposure assumptions and appropriate interpretations of the SF toxicological data all satisfy the minimum regulatory target of 100. The MOEs calculated and described within this document support the perspective of Vikane uses in the State of California as representing acceptable human inhalation exposure and risk potential when handled in conformance with product label directions and state regulations.

There are additional technical and policy issues in the RCD that are discussed in this document. Each of these issues has significant bearing on the regulatory decision-making associated with sulfuryl fluoride. Detailed explanations are provided in this document, referenced by the RCD page number and section. Refined margins of exposure based on more accurate and realistic exposure scenarios and toxicity values are also presented.

Sulfuryl Fluoride (Vikane™ gas fumigant) Use Pattern

Introduction

Sulfuryl fluoride (SF), the active ingredient in Vikane gas fumigant, is widely used for the control of dry wood termites (DWT). It is occasionally used (<2% of all treatments based on sales) to control other structural-infesting pests, such as wood-boring beetles (e.g. powder post beetles, PPB), cockroaches and rodents. Structures to be fumigated are typically sealed or enclosed with heavy nylon tarpaulins to confine SF, in order to maintain a maximum concentration and exposure within the fumigated structure. The structure generally remains sealed for approximately 18-24 hours followed by a minimum six to eight hour aeration period. During the aeration period, the tarpaulin is removed and the structure is initially actively aerated for a minimum of 1 hour with the use of natural ventilation and fans. The structure is then secured and passively aerated for the remainder of the six to eight hour period. Re-occupation into the fumigated structure by the resident is only permitted following this aeration period and after it has been confirmed that SF concentrations are at or below 5 ppm within the dwelling. If, at the end of the prolonged aeration period, ambient levels are measured at concentrations above 5 ppm, windows and doors are opened in the house for a second short period (a minimum of 10 minutes) at which point the SF concentrations are re-analyzed to determine whether SF concentrations are at or below 5 ppm prior to re-occupation.

Additionally, SF is occasionally used to control insect pests in shipping containers. This use occurs infrequently due to the existence of alternative fumigants such as methyl bromide and phosphine which have been specifically developed for this use.

Powder-Post Beetle Rate Calculations

There are several factors to consider when determining the appropriate scaling factor for adjusting potential exposure between those measured during the dry wood termite exposure studies (DWT fumigation rate is termed “submaximal” within the RCD) to those estimated for the control of PPB (SF uses rates termed “maximal” within the RCD).

Vikane fumigations are based on the following concept.

DOSAGE (ounce hours) = CONCENTRATION (C) X TIME (T)

DWT fumigations generally target a CT in the range of 100 oz hr/1000 ft^3 CT and PPB fumigations target a 10x CT dosage or about 1000 oz hr/1000 ft^3. Therefore, if a non-monitored PPB fumigation was going to be conducted for the same fumigant holding period as a DWT treatment, the DWT dosage would be calculated using all appropriate inputs to the Fumiguide* B and then multiplied by 10x to calculate the PPB dosage.

Using a high concentration of fumigant could be cost prohibitive due to the amount of fumigant required for the PPB treatment. Fumigators overcome this challenge in several ways. A common practice is to extend the time component of the CT product function. Companies can also reduce the target dosage, and thus the amount of fumigant needed, by monitoring the fumigation and/or postponing the fumigation until a warmer time of the year. Lengthening the fumigant holding period reduces the amount of fumigant required to obtain the desired CT. A representative range of typical DWT and PPB fumigations is provided in the following table.

Typical Use Rates, Holding Times, and Terminal Concentrations for Termite and Powder Post Beetle Fumigations in California.

	Termite Rate (1x rate)	Beetle Rate (10x rate)
Oz Hr Objective (CT)	60-100 oz hr	600-1000 oz hr
Initial Conc.	4-16 oz/MCF	40-80 oz/MCF
Holding Time	20-24 hrs	36-48 hrs
Typical Terminal Conc.	1-4 oz/MCF	8 - 14 oz/MCF

A 10x rate is not reflected in the initial concentration, but in the combined initial concentration x holding time CT. It is noteworthy to point out that the terminal concentrations in the monitoring studies submitted by DAS to DPR were approximately 10-12 oz/MCF. The terminal concentration levels from the DAS studies are about the same as the typical terminal concentrations of PPB fumigations. Thus, applying a 10x factor to exposure scenarios to represent PPB rates is inaccurate and misleading.

Below are additional comparisons of typical DWT to PPB SF "concentration" calculations assuming an unmonitored job with a 14 hr half-loss time (HLT) and a 36 hr exposure period for PPB vs. a 24 hr exposure period for DWT fumigations.

Temperature	DWT Conc. 24 Hr. Period (oz/1000 ft^3)	DWT Conc. 36 Hr. Period (oz/1000 ft^3)	PPB Conc. at 10x the 36 Hr. DWT rate (oz/1000 ft^3)	PPB Terminal SF Conc. [a] (oz/1000 ft^3)
65 ºF	11.2	9.3	93	16
70 ºF	9.3	7.8	78	13
75 ºF	7.9	6.6	66	11
80 ºF	6.9	5.8	58	10

[a] Approximately 30% would be remaining after 24 hr exp and 14 hr HLT; approximately 17% would be remaining after 36 hr exp. and 14 hr HLT.

This table of possible rate calculations for DWT and PPB fumigations suggest that the initial concentrations for the typical PPB fumigation compared to the rates used in the exposure studies (average Worker Exposure Study rate ~ 11 oz/1000 ft^3 and Bystanders ~16 oz/1000 ft^3) are about 4x to 8x that of the studied DWT rates. Terminal concentrations calculated for the typical PPB study are about 1-1.3x of the terminal concentrations aerated during the Bystander studies. Therefore the appropriate scaling factor for adjusting potential exposures between those measured during the dry wood termite DWT exposure studies to those estimated for a PPB fumigation is between 1x and 8x with a mean scaling factor of approximately 3.4X.

This scaling factor would be less if the dosing efficiencies of monitoring, warmer temperatures, and 48 hour fumigations were practiced for the infrequent and higher priced PPB jobs. It is important to note that PPB fumigations rarely occur in California, and only represent approximately 2% of the overall Vikane structural fumigations.

Duration of Exposures

Calculation of “short term”, “intermediate term” and “annual” absorbed daily dose (ADD) values for residents should not be necessary given their infrequent and short duration exposures. Acute exposures are the most appropriate endpoint to use for residents based on the air dissipation data and fumigation practices. The dissipation data shows a rapid loss of SF prior to and after clearance of the houses. Air concentrations are virtually undetectable after 2 days, the estimates of air concentrations beyond 2 days are simply a result of the modeling exercise with built-in conservative factors. Actual measurements show that SF air concentrations are often below the limit of detection after 2 days.

Frequency of Exposures

It is inappropriate to assume that residents are exposed to SF via house fumigations annually. Houses are typically fumigated once in 10 to 20 years or at the time of resale. A typical fumigation is initiated by a home inspection preparatory to sale. Following fumigation, approximately 10 years are required before dry wood termite populations reach a noticeable level and require re-treatment. Published data (Light, 1934) indicate that colonies of *Incisitermes minor* require at least 10 years to become established and grow to be detectable in infested structures. Incipient colonies of *I. minor* (n = 23) were extracted from infested wood following infestation by paired alates (king and queen) and rate of growth was found to be very slow. In a survey of 20 wooden oil derricks in CA, 60% (n = 12) were infested by *I. minor*. No oil derricks less than 10 years old were found to be infested with *I. minor*. The age of oil derricks infested with *I. minor* ranged from 10 to 26 years old (17 ± 6; mean ± SD).

Reference:

S. F. Light. 1934. Economic Significance of the Common Drywood Termite. *In* Termites and Termite Control. ed. C. A. Kofoid. University of California Press. Berkeley, CA. 734 pp.

The likelihood that an individual would be resident in a fumigated house either the day after fumigation or more than once in 10 years is extremely low. Therefore, there should be no short term, intermediate term, annual, or lifetime exposures for residents following fumigation of houses with SF. Similarly, there should be no short term, intermediate term, annual, or lifetime exposures for bystanders. Assuming annual fumigations overestimates resident and bystander exposures at least ten-fold.

Frequency of house fumigations

An informal survey of fumigation companies was done to provide information on the frequency of house fumigations and the frequency of repeated fumigations on the same house. Four companies in Southern CA were contacted that represent approximately 80% of house fumigations and provided responses to Dow AgroSciences. Based on responses below, coastal homes are more frequently fumigated than homes inland. This is presumed to be due to the greater humidity in the coastal region which is more conducive to termite colony development. A summary of survey results is given here:

Summary by company interviewed:

- Company 1: Estimates 10-12 yrs between fumigations of the same structure.
- Company 2: 8-10 yrs in coastal region, less often inland.
- Company 3: Estimates that houses are fumigated every 7-12 yrs in coastal areas, and 15-20 years inland.
- Company 4: Estimates that houses are fumigated every 15+ years.
- In summary, houses in California are not fumigated annually. Those that are fumigated are only fumigated every 7 to 20 years.

Relationship between Toxicological Studies for Sulfuryl Fluoride and Actual Exposures

	Acute	Short-Term	Intermediate	Annual	Lifetime
Duration of Exposure (RCD)	1 to 2 days	Up to 14 days	Up to 13 weeks	Up to a year	Lifetime
Appropriate NOEL	300 ppm	100 ppm (2 week rabbit)	30 ppm (13 week rabbit)	20 ppm (2 year rat)	20 ppm (2 year rat)
Occupational	Yes	Yes	Yes	Yes	Yes
Residential (re-entry)	Yes	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Bystander	Yes	Not Applicable	Not Applicable	Not Applicable	Not Applicable

Non-food commodity fumigations

Dow AgroSciences concurs with DPR's assessment that non-food commodity fumigations are infrequent. Worker exposure duration of 8 hrs/day with only one application per year is a realistic scenario for this uncommon use pattern.

Structural Worker Exposure Duration and Frequency

Several CA fumigation companies were contacted by phone to determine the length of career as: a) a crew member, or b) licensee for structural fumigation. Generally, the career as a crew member (putting tarps on, removing tarps, etc.) is limited to an average of 5-10 yrs due to the demanding physical labor involved, relatively low wages, and advancement to managerial positions. Career duration of licensees generally averages 10-15 yrs, which is longer than crew members, because pay is higher and work is less physically demanding. These observations in CA are reflected nationwide. According to U.S. Department of Labor, Bureau of Labor Statistics pest control workers must be in good health because of the physical demands of the job. They also must be able to withstand extreme conditions—such as the heat of climbing into an attic in the summertime or the chill of sliding into a crawlspace during winter. Many people do not find pest control work appealing and turnover in this occupation is high. Thus, in addition to job openings arising from employment growth, opportunities will result from workers who transfer or leave the occupation and need to be replaced. One factor limiting growth in this occupation, however, is the lack of workers willing to go into this field. Applicators with several years of experience often become supervisors.

Reference:
U.S. Department of Labor. *Occupation Outlook Handbook, 2004-2005.* Bureau of Labor Statistics.

While fumigation workers may work 5 days/week, it is unlikely they work 49 weeks/year for their entire career as fumigators. Weeks not spent fumigating are spent on vacation/holidays and work activities unrelated to fumigation, particularly during the “slow season”. A more realistic estimation would be 40-48 weeks per year or less that would be spent actually engaged in fumigation activities.

DOSE/RESPONSE AND HAZARD IDENTIFICATION

Toxic Air Contaminant Considerations

The RCD (*V.D.2. Reference Concentrations)* states that since bystander exposures showed MOES of less than 10,000, they exceeded the limit of no more than 1/10 the reference concentration, and therefore would meet the criteria for listing as a Toxic Air Contaminant under AB 1807. The conclusion from the RCD appears to be at odds with regulatory requirements. The California Code of Regulations Title 3 Section 6890 sets forth criteria for identifying pesticides as toxic air contaminants. The regulation specifies "A pesticide shall be identified as a toxic air contaminant if its *concentrations* in ambient air are …ten-fold below the air *concentration* which has been determined by the director to be adequately protective of human health". First, Dow AgroSciences questions whether air on a work site is ambient air, i.e., we do not believe this regulation is intended to apply to workers. Secondly, a specific ambient air concentration for regulatory purposes is not identified (there are several with varying durations of exposure and it is not clear which is the defining criteria for AB 1807).

Occupational Exposure

The RCD *(III.I.2.) Occupational Exposure* includes summaries of two studies of methyl bromide and sulfuryl fluoride fumigation workers in California (Anger *et al.*, 1986) and Florida (Calvert *et al*., 1998). Dow AgroSciences does not believe that either study demonstrates adverse health effects to fumigation workers.

Anger *et al*. (1986) suggest that their data argue "in favor of subjecting sulfuryl fluoride to further study." Given the absence of any statistically significant differences over about 70 endpoints, and the presence of small non-significant differences going in opposite directions (e.g., improved tactile sensitivity on one hand, vs. increased symptoms in lower extremities and decreased performance in cognitive tests on the other hand), and given the presence of confounders (participation bias, expectation bias) and the author's cautions in their discussion, the study **does not** support the statement that sulfuryl fluoride has any effects on any of the endpoints examined, including cognitive.

With regard to the paper by Calvert *et al***.** (1998), the results of this study of structural fumigant workers are better explained by bias, confounding or chance than by exposure to fumigants. This is especially true since the authors indicate that the exposure to sulfuryl fluoride, based on a 1991 NIOSH study, was non-detectable or below the Occupational Safety and Health Administration permissible exposure limits. Additionally, the study observed no more statistically significant positive findings than would be expected given the large number of comparisons made. In light of the above mentioned weaknesses and inconsistencies, the current study does not show an adverse health effect due to long-term low level exposure to sulfuryl fluoride.

Detailed comments for the two fumigation worker studies (Anger *et al.*, 1986; Calvert *et al*., 1998) are provided in the following sections.

Neurobehavioral Evaluation of Soil and Structural Fumigators Using Methyl Bromide and Sulfuryl Fluoride. Anger, W.K., Moody, L., Burg, J., Brightwell, W.S., Taylor, B.J., Russo, J.M., Dickerson, N., Setzer, J.V., Johnson, B.L. and Hicks, K. NeuroToxicol. 7: 137-156, 1986.

<u>Study summary</u>. Three groups of fumigators exposed to methyl bromide (N=32), sulfuryl fluoride (N=24) or to a combination of both (N=18) were compared to a referent group (N=29) composed of workers who had a job related to the fumigation industry, but were not directly exposed to fumigants on a regular basis (a chemist, fumigation tank fillers, salespeople, supervisors, owners and state specialists or inspectors). The subjects were examined blind to treatment; however, the blind procedure was not effective as reported by the authors (p. 142). The following functions/tests were evaluated: general symptoms, nerve conduction velocity/peroneal, grip strength, eye-hand coordination, nerve conduction velocity/ulnar, vibration sensitivity, tactile depth discrimination, two-point discrimination, electromyogram, eyeblink reflex, visual depth discrimination, Wechsler memory scale, digit symbol substitution, trailmaking, attention test. Fumigators using methyl bromide reported a significantly higher prevalence of symptoms consistent with toxicity than the control group, and did not perform as well as the controls on 23 of 27 behavioral tests. As far as the fumigators exposed to sulfuryl fluoride were concerned, they had slightly but not significantly decreased scores on some cognitive tests compared to the control group.

<u>Dow AgroSciences Comments</u>: Most of the fumigant workers used both methyl bromide and sulfuryl fluoride. The mean estimated use of sulfuryl fluoride by the methyl bromide group was 8% (see Table 3 of publication). However, no information is provided if *all* methyl bromide workers also used sulfuryl fluoride. The following analysis will focus only on the sulfuryl fluoride data.

The authors reported <u>no statistically significant difference between the control and sulfuryl fluoride exposed groups</u> for the following endpoints:

1. **Overall comparisons**
    a. symptoms
        i. Ss reporting one or more in past month
        ii. Ss reporting one or more since entering occupation
2. **General**
    a. symptoms
        i. muscle aching
        ii. muscle fatigue
        iii. coordination problems
        iv. depression

        v. slurred speech
        vi. dizziness

3. **Gait and station**
    a. symptoms
        i. stumbling when walking
        ii. weaving and staggering
    b. neurological exam
        i. walking
        ii. tandem walking
        iii. standing/eyes open
4. **Lower extremity/motor and reflexes**
    a. neurological exam
        i. walk on heels, toes
        ii. heel to shin
        iii. knee reflexes
        iv. ankle reflexes
    b. nerve conduction velocity/peroneal
        i. standardized nerve conduction velocity
        ii. standardized distal latency
5. **Lower extremity/sensory**
    a. symptoms
        i. tingling in feet
        ii. numbness in feet
    b. neurological exam
        i. standing/eyes closed
        ii. position sense in toes
        iii. vibration sense in toes
6. **Upper extremity/motor**
    a. symptoms
        i. muscle weakness in hands
        ii. hand tremor
    b. neurological exam
        i. grip strength
        ii. arms out/eyes closed (with drift)
        iii. write sentence
        iv. pronation/supination hands
        v. fingers/thumb
        vi. touch nose with forefinger
        vii. finger/nose/finger
        viii. arms out/eyes closed (with tremor)
        ix. biceps reflexes
        x. brachial/radial reflexes
    c. nerve conduction velocity/ulnar
        i. standardized nerve conduction velocity
        ii. standardized distal latency
    d. dynamometer
        i. grip strength
        ii. fatigue
    e. Michigan Eye-Hand coordination
        i. time to complete test
        ii. standard deviation of hole to hole time
7. **Upper extremity/sensory**
    a. symptoms
        i. tingling in hands
        ii. numbness in hands
    b. neurological exam

i. position sense/fingers
ii. vibration sense/fingers

c. optacon
   i. threshold
d. tactile depth discrimination
   i. threshold
e. two-point discrimination
   i. threshold

8. Visual signs and symptoms/extraocular movements

a. symptoms
   i. blurred vision
   ii. focus problems
   iii. eye twitches
   iv. wear glasses
b. neurological exam
   i. nystagmus
c. electromyogram
   i. amplitude
d. eyeblink reflex
   i. prepulse/baseline ratio amplitude
   ii. prepulse/high latency ratio
   iii. prepulse/low latency ratio
e. orthorater
   i. visual depth discrimination
   ii. acuity, far/worst eye
   iii. acuity, near/worst eye
   iv. acuity, far/both eyes
   v. acuity, near/both eyes

9. Cognitive effects

a. neurological exam
   i. objects recalling
b. Wechsler memory scale
   i. number of facts recalled
c. Digit symbol
   i. correct matches
d. trailmaking A
   i. time to complete
   ii. number of errors
e. trailmaking B
   i. time to complete
   ii. number of errors
f. Bourdon Wiersma
   i. correct strikeouts

The sulfuryl fluoride group had more symptom-positive reports in the lower extremities than the referents; however, it performed better than the referent group on all three tests of tactile sensitivity (i.e., vibration sensitivity, tactile depth discrimination and two-point discrimination). A statistically nonsignificant reduced performance in all cognitive tests was found in the sulfuryl fluoride group compared to the control group in the presence of a nonsignificant increase of illegal drug use and of drinks per week, and decrease in educational level in the sulfuryl fluoride group compared to the control group (see Table 4, page 146). The cognitive data are summarized in the table below. The magnitude of the differences between control and sulfuryl fluoride groups in these cognitive tests ranged approximately from a twentieth to a third of one standard deviation.

Cognitive Tests	Referent Group (Mean)	Sulfuryl Fluoride Group (Mean)	Referent Standard Deviation	Difference between means expressed in Referent Standard Deviations
Wechsler Memory Scale	21	19	7	0.29
Digit Symbol	58	54	12	0.33
Trailmaking A	27	28	9	-0.11
Trailmaking B	74	76	34	-0.06
Bourdon-Wiersma	286	279	39	0.18

The authors start their discussion by warning the reader about the lack of information concerning the participation bias that would have encouraged the workers who present medical problems to participate in the study (although they do not have any evidence for this). They continue warning the reader about "a welter of potentially biasing factors that cannot be satisfactorily unraveled." (p. 153), including expectation bias (i.e., the awareness of chemical exposure will result in over-reporting of symptoms and will cause the subjects to perform below their ability).

The 29 Referents were defined as employees of the fumigation company but not as active fumigators. Compared to the 24 sulfuryl fluoride fumigators, the Referents were older (mean age 36 vs. 31), better educated (96% vs. 86% had > 8 years), and used less illicit drugs and alcohol. The Referent group is known to have a more sedentary and less strenuous job than the structural fumigators (page 153). With these known differences, suggesting additional unmeasured differences, the Referent group is an inappropriate control group for this study. The results presented in Table 5 – 10 are crude means that do not represent data adjusted for the measured differences in the two groups. Uncontrolled differences reflect the underlying differences in the Referent group as shown in Table 4. When statistical adjustments were made, there were no significant differences between the sulfuryl fluoride fumigators and the controls.

The authors suggest that their data argue "in favor of subjecting sulfuryl fluoride to further study." (page 154). Given the absence of any statistically significant differences over about 70 endpoints, and the presence of small nonsignificant differences going in opposite directions (e.g., improved tactile sensitivity on one hand, vs. increased symptoms in lower extremities and decreased performance in cognitive tests on the other hand), and given the presence of confounders (participation bias, expectation bias, …) and the author's cautions in their discussion, we conclude that the study **does not** support the statement that sulfuryl fluoride has any effects on any of the endpoints examined, including cognitive.

Health Effects Associated With Sulfuryl Fluoride and Methyl Bromide Exposure Among Structural Fumigation Workers. Calvert G.M., Mueller, C.A., Fajen, J.M., Chrislip, D.W., Russo, J., Briggle, T., Fleming, L.E., Suruda, A.J., and Steenland, K. Amer J Public Health 88: 1774-1780, 1998.

Study summary. The Calvert *et al*. study is a cross sectional study of workers employed at the time of the study in the structural fumigation industry. Exposure to methyl bromide or sulfuryl fluoride was defined by the years employed and the percent of jobs in the past year using methyl bromide or sulfuryl fluoride. The referent subjects were friends or neighbors of the exposed subjects.

Fumigation workers performed worse on tests of median nerve function than did the referents. The authors attributed this finding to ergonomic stresses of the job. A trend of worse performance in Pattern Memory with increasing lifetime duration of sulfuryl fluoride was observed. A significant deficit of olfactory function as measured by UPSIT performance among the high sulfuryl fluoride exposed workers also was observed.

Dow AgroSciences Comments: The Calvert *et al*. study is a relatively large study of fumigant workers with good attention to study design, methodology and data analysis. The use of friend controls was appropriate for this mostly immigrant population. The data are presented well, and the tables in the paper are comprehensive, in that they show all the endpoints under study. However, there are some weaknesses to the study due to poor exposure determination, cross-sectional design, control of error rate and cultural sensitivity of the UPSIT.

The exposure measure for this study was a component of years worked in the fumigation industry and proportion of fumigation jobs that used methyl bromide (or sulfuryl fluoride). This is not a true indication of *exposure*. There is no distinction between *exposure* and *use*. In fact, the exposure measure is merely a marker for employment in a physical and potentially stressful job, which may completely explain the differences between the fumigation workers and referents. The authors state in their discussion section that the fumigant exposure among structural fumigation workers is low based on personal airborne sampling conducted by NIOSH in 1991. The NIOSH study showed that all personal airborne sampling results for sulfuryl fluoride were below the Occupational Safety and Health Administration permissible exposure limits (20 mg/m^3 {5 ppm}time-weighted 8-hour average). Furthermore, the NIOSH study showed that more than two thirds of the measurements were below the limit of detection for sulfuryl fluoride (0.007 mg/sample). Thus, the lack of significant or even measurable exposure of structural fumigation workers as represented by the NIOSH study suggests that the results of the Calvert et al. (1998) study should be attributed to factors other than sulfuryl fluoride.

The Calvert *et al*. study relies upon the differences between workers and referents in test performance on a single day. The study was not designed to determine if reductions in performance were pre-existing to the study period. The referent group was younger, more educated, fewer Spanish speakers, and consumed less alcohol and tobacco. These factors were adjusted in the statistical models. Since this study was cross-sectional, other pre-disposing, unmeasured differences between the groups may explain the differences in their neurobehavioral performance.

The authors controlled the Type I error rate at 0.05 per comparison. However, a large number of *p* values (about 115 *p* values) were derived, and there were 9 statistically significant *p* values. According to Gill (1985)[1], the minimum number of statistically significant tests (at alpha = 0.05) required for 95% confidence that a true difference exists for one or more out of 115 traits is 10, i.e. the 9 significant differences could simply be explained by the false positive rate associated with the total number of comparisons. If some statistically significant differences are deemed to be true positives due to an emerging pattern, for example, the case can be made that the effect is a true effect (the next question being whether the effect size has biological significance).

The authors correctly attribute the positive findings for the median nerve motor conduction velocity and Santa Ana dexterity test (preferred hand) to workplace ergonomic factors rather than exposure to the fumigants. The authors mention that the one median nerve outcome (nerve conduction velocity of the median motor nerve in the forearm) associated with exposure to sulfuryl fluoride "may be an isolated chance finding caused by the large number of comparisons that were performed."

Reduced performance on the Pattern Memory test appears to be the only positive finding of potential memory effects. However, the other endpoints related to memory are all negative for an association, i.e. Pattern Memory recall time, Symbol Digit, Symbol Digit recall score, Serial Digit Learning score. Thus, the observed effect is unlikely to be a *true* exposure-related effect. In fact, the authors state that "…the pattern memory findings may have arisen by chance."

Some comment on this test is warranted. The UPSIT is not a culture-free test. For example, pumpkin pie, gingerbread, wintergreen, chili, licorice, dill pickle and root beer are very much part of the US culinary armamentarium and culture. Some people with a higher education may more easily recognize musk, leather and cedar than people with only a few years of schooling. These odors were presented in the original test, as described in 1984.[2] While the exact odors of the UPSIT in the current study were not

[1] Gill. Interpretation of significance in testing multiple traits. J. Anim. Sci. 1985;60:867-869.

[2] Doty et al. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol. Behav. 1984;32:489-502.

provided, differences in odor recognition among the study subjects may have more to do with acclimation to US culture than with exposure.

The study did not find significant associations with exposure for vibration testing, the NES vocabulary test, postural sway testing, and contrast sensitivity. Furthermore, measures of urinary total protein, albumin and adenosine deaminase binding protein were normal which suggest no effect on kidneys. Also, no significant differences were found between fumigation workers and referents for chronic bronchitis based on questions recommended by the American Thoracic Society.

The Calvert *et al*. study is a relational study. The investigators categorized subjects' sulfuryl fluoride exposure in relation to their methyl bromide exposure. In the context of understanding potential health risks from sulfuryl fluoride exposure, the results for the high methyl bromide exposed group are equally important because *all* of the high methyl bromide subjects were also 'exposed' to sulfuryl fluoride. For example, the two statistically significant deficits among the high-exposure sulfuryl fluoride workers, the olfactory test (UPSIT) and the pattern memory test, were marked by *better* performance among the high-exposure methyl bromide workers.

The results of Calvert *et al*. study of structural fumigant workers are better explained by bias, confounding or chance than by exposure to fumigants. This is especially true since the authors indicate that the exposure to sulfuryl fluoride, based on a 1991 NIOSH study, was non-detectable or below the Occupational Safety and Health Administration permissible exposure limits. Additionally, the study observed no more statistically significant positive findings than would be expected given the large number of comparisons made. In light of the above mentioned weaknesses and inconsistencies, the current study **does not** show an adverse health effect due to long-term low level exposure to sulfuryl fluoride.

Selection of Endpoints

The RCD (IV.A.1.) should include additional comments on the significance of fluoride in regard to sulfuryl fluoride toxicity. The pharmacokinetic study with sulfuryl fluoride (Mendrala *et al*., 2002) indicated that no parent sulfuryl fluoride would be expected in blood. Inhaled sulfuryl fluoride is hydrolyzed to flurosulfate and ionic fluoride followed by further hydrolysis to sulfate and an additional fluoride ion. Based on studies with hydrogen fluoride, the initial hydrolysis of sulfuryl fluoride is likely to occur in respiratory tissues, especially nasal tissues.

Studies in rats with hydrogen fluoride indicate that virtually all inhaled hydrogen fluoride deposits in the upper respiratory tract and that plasma fluoride concentrations were significantly elevated by exposure to the isolated upper respiratory tract (Morris and Smith, 1982). This publication discusses the dissolution of inhaled gas molecules in the fluid lining layer of the upper respiratory tract. Once in solution, diffusion away from the lining layer occurs. Removal of gaseous solutes in the bloodstream or through chemical reaction will push the equilibrium toward the liquid phase. The authors cite the irritant compounds ammonia and sulfur dioxide (SO2) as examples of highly water soluble compounds (suggestive of high solubility in tissue fluids) that also are reactive with water. Other studies are cited by Morris and Smith (1982) that indicate these two compounds have upper respiratory tract deposition efficiencies of 95% or greater. The experimental work with HF and SO2 thus provide a basis to suggest the respiratory tract as the site of initial hydrolysis of SO2F2.

The inflammation in the respiratory tissues, especially the nasal tissues, of animals repeatedly exposed to sulfuryl fluoride for 6 hr/day, 5 days/wk reflects the irritant properties of sulfuryl fluoride on the respiratory system.

The RCD further states that "…the absence of fluorosis in mice after subchronic (Nitschke *et al.*, 1987a) and chronic [sic] (Quast *et al.*, 1993b) suggested that brain lesions could occur in the absence of fluoride." In fact, the subchronic study in mice (Nitschke *et al.*, 1987a) included measurement of serum fluoride which was increased in males and female mice in a dose-response relationship (see Table 88.1, Nitschke and Eisenbrandt, 2001). Statistically significant increases in serum fluoride were demonstrated in female mice exposed to 30 ppm sulfuryl fluoride and male and female mice exposed to 100 ppm for 13 weeks; the 100-ppm group of mice also had vacuolation in the cerebrum. Since the 13-week mouse study demonstrated the elevation of serum fluoride in mice and because the 18-month mouse study (Quast et al., 1993b) is primarily an oncogenicity study, serum fluoride was not measured on the 18-month mouse study.

A discussion of the similarities between sulfuryl fluoride toxicity and fluoride toxicity is included in the publication by Eisenbrandt and Nitschke (1989).

References:

Eisenbrandt, D. L. and Nitschke, K. D. 1989. Inhalation toxicity of sulfuryl fluoride in rats and rabbits. Fundam. Appl. Toxicol. 12: 540-557.

Morris, J. B. and Smith, F.A. 1982. Regional Deposition and Absorption of Inhaled Hydrogen Fluoride in the Rat. Toxicol. Applied Pharmacol. 62: 81-89.

Nitschke, K.D. and Eisenbrandt, D.L. 2001. Sulfuryl Fluoride. In Handbook of Pesticide Toxicology, Second Edition, Volume 2. R. Krieger, Ed. Academic Press, San Diego, pp. 1881-1896.

Selection of No-Observed-Effect Levels: Acute Toxicity

The RCD (IV.A.2.a and IV.A.3) indicates that the acute NOEL was selected from a 2-day inhalation study (6 hours/day) specifically designed to evaluate the neurotoxicity of sulfuryl fluoride. At the highest dose (300 ppm) tested, there were no treatment-related effects observed (Albee *et al*., 1993 a and b). The RCD notes that there is an issue in regard to the derivation of a one-day NOEL and the application of this NOEL for the MOE calculation. DPR calculates the NOEL for 24-hour exposure using the single day NOEL from the study, as shown below:

$$300\ ppm \times \frac{6\,hours}{24\,hours} = 75\ ppm$$

Dow AgroSciences agrees with the selection of the 2-day neurotoxicity study for the acute toxicity endpoint as well as the NOEL of 300 ppm for this study. However, DPR calculated a 24-hour exposure NOEL using the single day NOEL from the acute study but, in fact, the study design did not include any evaluations after the first exposure and thus, there was no basis for a single-day NOEL. Furthermore, the calculation of the dose-time relationship in the RCD significantly underestimates the relevant internal dose to the rats and thus underestimates the MOE for humans.

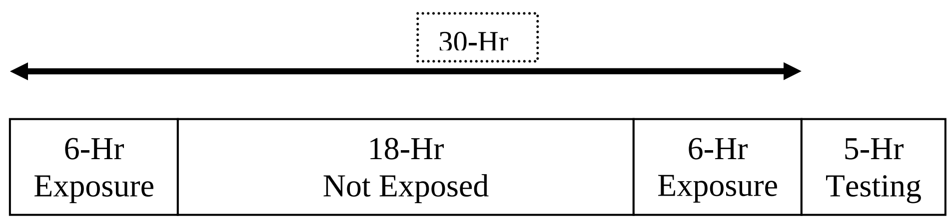
The two-day acute study was specifically designed to evaluate neurotoxicological end points immediately following the second of two daily exposures that were expected to result in a cumulative internal dose greater than a single 4-hr exposure. The acute NOEL of 300 ppm from the two-day, rat acute inhalation neurotoxicity study is appropriate for bystanders and also relevant to reoccupation of structures after clearance for reentry.

The acute neurotoxicity study was required in a November, 1992 Data Call-In by the U.S. EPA. The study protocol was designed jointly by Dow AgroSciences and the U.S. EPA (EPA Memoranda, July 31, 1992 and Oct 8, 1992, from L.J. Hansen, Health Effects Division to L. Rossi, Reregistration Branch) in order "...to provide more accurate NOELs for short-term exposure to sulfuryl fluoride."

Repeated, daily, inhalation exposures with sulfuryl fluoride result in elevation of serum fluoride as well as cumulative toxicity which differs from a single exposure. Repeated exposures of rabbits (6 hr/day, 5 days/wk) to 300 or 600 ppm sulfuryl fluoride for two weeks resulted in cerebral malacia (necrosis). Also, repeated exposures of rats to 300 ppm for 13 weeks results in vacuolation in the brain as well as clear electrophysiological changes in evoked potentials. Importantly, evoked potential changes were detectable in the absence of vacuoles in the rats exposed to 100 ppm. On the grounds that neurophysiological changes would be expected to precede neuropathological lesions, Dow AgroSciences and the U.S. EPA agreed to a modified acute neurotoxicity protocol to examine rats for functional changes from the cumulative effects of two, 6-hr exposures.

The modified acute neurotoxicity guideline study was intended to meet the objectives of the acute neurotoxicity testing requirements of the EPA neurotoxicity guideline (EPA, 1991). The EPA specified that the “Rats should be exposed to sulfuryl fluoride for 2 consecutive days, 6 hrs/day rather than the typical acute single 4 hr exposure.” The EPA’s rationale for the modified duration indicated that “Inhabitants of houses <u>may</u> be exposed to low levels of sulfuryl fluoride over 1 - 2 days…” and also "The proposed exposure period [6 hrs/day for two days] should provide a more reasonable estimation of risk from short-term exposure to sulfuryl fluoride than is presently available."

The study design for the two-day rat neurotoxicity study utilized an initial 6-hr exposure to sulfuryl fluoride, followed by 18-hr non-exposure, followed by a second 6-hr exposure to sulfuryl fluoride. Thus, there were two 6-hr exposures within a 30-hr time period. The critical neurotoxicological evaluations (electrodiagnostics and functional observational battery) were conducted within 5 hr after the second exposure. The electrodiagnostic evaluations were initiated 1.5 hrs post exposure and were completed by 4.4 hrs post exposure. The functional observational battery evaluations were initiated 0.7 hrs post exposure and completed by 1.4 hrs post exposure. The non-specific, less sensitive motor activity testing was initiated at 18 hrs post exposure and completed at 19 hrs post exposure.



Inherent in this cumulative-dose study design are the two, 6-hr exposures that occurred within a 30-hr (1.25-day) time period. Thus, the calculated internal dose of sulfuryl fluoride for the rats should be based on the total internal dose from both 6-hr exposures. The internal dose during the 30-hr (1.25-day) period was 708.7 mg sulfuryl fluoride/kg body weight based on the actual average body weight of 0.1435 kg for the rats on the study and an inhalation rate of 0.1626 m^3/day ($I = 0.80\ W^{0.8206}$; Blackburn, K. Recommendations for and Documentation of Biological Values for Use in Risk Assessment, ORD, U.S. EPA, Cincinnati, OH, EPA/600/6-87/008, 1988). This calculation assumes 100% absorption.

$$300\ ppm \times 4.17 \times \frac{0.1626\, m^3}{day} \times 1.25\, days \times \frac{0.5\, day\ exposure}{1.25\, day\ time\ period} \div 0.1435\ kg = 708.7\, mg/kg$$

The potential exposure to bystanders is consistent with the exposure scenario used in the two-day acute neurotoxicity study (Albee *et al.*, 1993). The data presented in the home fumigation study (Barnekow *et al*., 2002) revealed that the potential exposure to bystanders occurs at two time intervals with a decline to low or no exposure between the two exposures intervals. The initial exposure interval was at fumigant introduction followed by a decline to background or near background levels within 8 hours. The second potential exposure occurs for approximately 2 hour at the initiation of aeration followed by an immediate drop to background (not detectable: ½ LOD = 0.01 ppm).

Since potential bystander exposures from fumigation and aeration occur within a 30-hr time period, the total exposure from the two-day acute neurotoxicity study is relevant and appropriate for bystander risk assessment. As indicated by the U.S. EPA (above), the 30-hr time period also is a reasonable surrogate for reoccupation of homes after clearance to very low levels of fumigant. The total internal dose to the rats from both of the 6-hr exposures within the 30-hr (1.25-day) exposure scenario was scaled to a 24-hr potential human exposure in order to correspond to the 24-hr time-weighted average data utilized for bystander exposure estimates (Wright et a*l*., 2003). Thus a more accurate NOEL determination for 24 hour exposure would be as follows:

708.7 mg/kg body weight/1.25 days = 567 mg/kg body weight/day

Recent research by the Neurotoxicology Division of NHEERL, U.S. EPA, indicates that internal tissue dose better predicts a constant biological effect than simple exposure concentration times duration and is thus more relevant for human risk assessment (Evans *et al*., 2002; Boyes *et al*., 2003). This appears to be especially true for short-term durations of exposure as compared to chronic exposures. The classic form of Haber’s rule is a linear product: concentration multiplied by the exposure duration results in constant biological effect ($C \, x \, t = k$). Haber’s rule is widely used due in part to its mathematical simplicity and applicability to different chemicals and is often assumed to be applicable across different inhalation exposure durations. However, the recent EPA studies indicate that a traditional linear expression of Haber’s rule was inadequate to predict neurotoxicity across exposure durations. A better predictor of toxicity is to understand the target tissue concentrations such as provided by, for example, physiologically based pharmacokinetic (PBPK) models.

Although PBPK modeling for sulfuryl fluoride is not available, Dow AgroSciences has submitted to DPR an inhalation pharmacokinetic study (Mendrala *et al*., 2002). The results of the pharmacokinetic study suggest that sulfuryl fluoride toxicity is the result of metabolic release of fluoride ions. The data from the pharmacokinetic study and the repeated-exposure studies support the cumulative toxicological results from repeated, daily exposure to high levels of sulfuryl fluoride. In regard to the 2-day, acute neurotoxicity study, fluoride levels from the first 6-hr exposure, to some degree, would be expected to persist in some tissues for several hours following exposure. Thus, the internal dose of sulfuryl fluoride that results from both 6-hr exposures should be taken into consideration for the acute NOEL since both exposures would have contributed to any evidence of neurological effects.

Dow AgroSciences recommends that acute risk assessments utilize a NOEL of 300 ppm from the 2-day rat acute inhalation neurotoxicity study with an internal dose from both exposures (within a 30-hr time period) calculated at 708.7 mg/kg body weight. The relevant dose-time conversion for the 30-hr time period scaled to a 24-hr potential human exposure (correspond to the 24-hr time-weighted average data utilized for bystander exposure estimates) is 24/30 hr resulting in an internal dose NOEL of 567 mg/kg body weight per day.

<u>References:</u>

Boyes, W.K., Bercegeay, M., Ali, J.S., Krantz, T., McGee, J., Evans, M., Raymer, J.H., Bushnell, and Simmons, J.E. Dose-based duration adjustments for the effects of inhaled trichloroethylene on rat visual function. Tox. Sci. 76: 121-130, 2003

Evans, M.V., Boyes, W.K., Simmons, J.E., Litton, D.K., Easterling, M.R. A comparison of Haber’s rule at different ages using a physiologically based pharmacokinetic (PBPK) model for chloroform in rats. Toxicology. 176: 11-23, 2002

Mendrala, A.L., Markham, D.A., Clark, A.J., Krieger, S.M., Houtman, C.E. and Rick, D.L. Sulfuryl fluoride: Pharmacokinetics and metabolism in Fischer 344 rats, May 22, 2002.

Calculations from No-Observed Effect Levels (NOEL)

<u>Dosage Normalization:</u>

The RCD is inconsistent in normalizing animal exposure vs. human exposure. Appendix D.7. provides the calculation for the reference concentration in ppm. The reference concentration is calculated by first determining the human equivalent NOELs by the following equation. This equation includes the normalization of the exposure to 7 days (number of days exposed/7 days a week). If normalization is needed in the conversion of animal NOELs to human NOELs for short term, subchronic and chronic potential exposures then the two terms used in the conversion of the NOELs must be accounted for in the calculation of exposure estimates.

$$ADD = \frac{AD_i \times daily\ duration\ (hr/day) \times days\ potentially\ \text{exposed}\ (days/week)}{7\ (days/week) \times body\ weight\ (kg)}$$

$$MOE = \frac{NOEL\ (mg/kg/day)}{Human\ Exposure\ (mg/kg/day)}$$

Example Calculations:

(Fumigators worker – HS-1834, pp. 26-28, Tables 5, 6 and 7a)

Short-term = Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)}{7\ (days/week) \times 70\ kg} = 0.0046\ mg/kg/day$$

MOE = (40 mg/kg/day) ÷ (0.0046 mg/kg/day) = 8,695

Subchronic = Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)}{7\ (days/week) \times 70\ kg} = 0.0046\ mg/kg/day$$

MOE = (12 mg/kg/day) ÷ (0.0046 mg/kg/day) = 2,608

Chronic = Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)\ 208\ (days/year)}{7\ (days/week)\ 365\ (days/year) \times 70\ kg} = 0.00026\ mg/kg/day$$

MOE = (16 mg/kg/day) ÷ (0.00026 mg/kg/day) = 61,538

Lifetime= Geometric Mean Air Concentration of 0.08 ppm

$$ADD = \frac{0.33 \times 0.17\ (hr/day) \times 4\ (days/week)\ 208\ (days/year)\ 40\ (working\ years)}{7\ (days/week)\ 365\ (days/year) \times 70\ (years\ lifetime) \times 70\ kg} = 0.00015\ mg/kg/day$$

MOE = (16 mg/kg/day) ÷ (0.00015 mg/kg/day) = 106,667

Calculation of Reference Concentration:

The RCD (*Appendix D*) provides the method for calculating the reference concentration; first by determining the dosage in animals equivalent NOEL and the secondly by determining the dosage in humans (specifically children). Using the child specific respiration rate adjusts for the difference in inhalation rate to body weight ratio differences between species. This specific correction for children is appropriate for exposure scenarios in which children are potentially exposed (acute exposures to the fumigation or re-entry of an aerated structure), but the calculation of the reference concentration using a child-specific respiration rate is not applicable to durations of exposure that do not exist for the child, i.e., short term (in this case 2 week), intermediate term and annual.

Mammalian Pharmacokinetics and Metabolism (ADME)

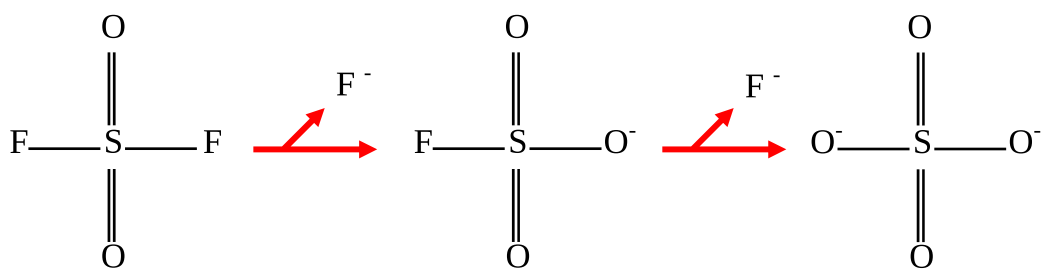
The RCD (III.A.) includes comments on the Dow AgroSciences' pharmacokinetics study. The Dow AgroSciences metabolism study indicates a lack of systemic exposure to sulfuryl fluoride and indicates that the systemic toxicity of this fumigant is due to fluoride. The pharmacokinetics and metabolism of inhaled SO_2F_2 were evaluated in male Fischer 344 rats exposed to 30 or 300 ppm ^{35}S-labeled SO_2F_2 for 4 hr. Blood, urine and feces were collected during and after the exposures and analyzed for radioactivity as well as ^{35}S-labeled fluorosulfate and sulfate, and fluoride (urine and feces only). Selected tissues were collected 7 days post-exposure and analyzed for radioactivity. In addition, during and after exposures to unlabeled SO_2F_2, blood, brain and kidney were collected and analyzed for fluoride ion.

SO_2F_2 was rapidly absorbed via inhalation exposure, achieving maximum concentrations of radioactivity in both plasma and red blood cells (RBC) near the end of the 4 hr exposure period. Radioactivity was rapidly excreted, mostly via the urine as fluorosulfate and sulfate. Seven days post-exposure, small amounts of radioactivity were distributed among several tissues, with the highest concentration detected in respiratory tissues. Radioactivity associated with the RBC remained elevated 7 days post-exposure and highly perfused tissues had higher levels of radioactivity than other non-respiratory tissues. The radioactivity present in tissues suggests some incorporation of the ^{35}S via normal sulfate pool metabolism. Radioactivity cleared from plasma and RBC with initial half-lives of 2.5 h after 30 ppm and 1-2.5 h after 300 ppm exposures. The terminal half-life of radioactivity was 2.5-fold longer in RBC than plasma.

Sulfuryl fluoride is rapidly removed from rat blood fortified *in vitro* with high levels of sulfuryl fluoride ($t_{½}$<3 min) and is rapidly hydrolyzed in aqueous solutions ($t_{½}$<18 min at pH=8.0). Thus, no parent sulfuryl fluoride in blood or urine would be expected due to rapid hydrolysis. Based on the radiochemical profiles in the ADME study, there was no evidence of parent ^{35}sulfuryl fluoride in the blood. Identification of fluorosulfate and sulfate in blood and urine suggests that sulfuryl fluoride is hydrolyzed to fluorosulfate, with release of fluoride, followed by further hydrolysis to sulfate and release of the remaining fluoride. This metabolism is supported by the increases in fluoride detected in the blood and urine following exposure of rats to sulfuryl fluoride. The sulfuryl fluoride ADME study supports the hypothesis that sulfuryl fluoride toxicity is the result of metabolic release of fluoride ions rather than a direct toxic action of sulfuryl fluoride.

Key conclusions from the metabolism study are as follows:

- No measurable parent sulfuryl fluoride would be expected in blood or urine due to rapid hydrolysis.
- Inhaled sulfuryl fluoride is hydrolyzed to fluorosulfate and ionic fluoride followed by further hydrolysis to sulfate and an additional fluoride ion:



Sulfuryl fluoride   Fluorosulfate   Sulfate

- Fluoride ion was rapidly excreted in the urine.
- No indication that sulfuryl fluoride, fluorosulfate, or fluoride bioaccumulate in soft tissues following inhalation exposure to sulfuryl fluoride.
- The data suggest that the systemic toxicity elicited by sulfuryl fluoride is due to the release of fluoride ions, rather than a direct toxic action of sulfuryl fluoride.

An absorbed dose was estimated based on measured internal dose from radioactivity as compared to internal dose estimated from inhalation rate and body weight. The estimated absorbed dose was 14.1% or 12.4%, respectively, for exposure concentrations of 30 ppm and 300 ppm. However, internal dose calculations for purposes of risk assessment were based on the default of 100% absorption.

In summary, the metabolism study of sulfuryl fluoride indicates a lack of systemic exposure to sulfuryl fluoride due to rapid hydrolysis. The data also suggest that the systemic toxicity of sulfuryl fluoride is due to the release of fluoride ions rather than a direct toxic action of sulfuryl fluoride. Thus, risk assessments related to the restricted use patterns and relatively low levels of potential human exposure to sulfuryl fluoride gas would be similar to the available evaluations for fluoride.

Reference:

Mendrala, A.L., Markham, D.A., Clark, A.J., Krieger, S.M., Houtman, C.E. and Rick, D.L. Sulfuryl fluoride: Pharmacokinetics and metabolism in Fischer 344 rats, May 22, 2002.

Selection of No-Observed Effect Levels for Chronic Toxicity

The RCD (IV.A.2.d. and IV.A.3) states that the critical NOEL was 4 mg/kg/day (5 ppm) in rats for dental fluorosis in a chronic toxicity study and for lung inflammation and alveolar macrophage aggregates in a 2-generation reproductive toxicity study. The respiratory system effects were considered the critical effect for chronic inhalation exposure and the chronic reference concentration. DPR indicates that the NOEL of 5 ppm for the two-generation reproduction study is based on increased alveolar macrophages in the lungs of rats exposed to 20 ppm. Risk assessments must take into consideration that the rats on the reproduction study actually were exposed for 6 hours/day, **7 days/week during mating, gestation and lactation** through two generations. The 7-days/week inhalation exposures of the rats during these critical phases of the reproduction study were intended appropriately to maximize the opportunity to detect possible adverse effects on reproduction. However, the extended period of 7-days/week exposures for the rats on the reproduction study are not representative of potential human chronic exposures to SF.

The increase in alveolar macrophages in animals exposed long-term to sulfuryl fluoride is a manifestation of the irritancy properties of sulfuryl fluoride to the respiratory tract and is a portal of entry effect rather than a systemic effect. In contrast to the increase in alveolar macrophages in the lungs of rats exposed to 20 ppm for 7-days/week for an extended period on the reproduction study, lungs of rats, mice or dogs exposed to 20 ppm sulfuryl fluoride 5 days/week for 12, 18 or 24 months did not have alveolar histiocytosis or other effects. Since 5-days/week exposures more closely approximates the potential human exposure for workers, the NOEL of 20 ppm from the chronic studies with rats or dogs is more appropriate for repeated-exposure risk assessments.

Dental fluorosis in humans is detected by clinical examination. On the other hand, macroscopic dental fluorosis was not evident in either the 1-year dog or the 2-year rat study at any dose level during in-life phases or at necropsy. In the 1-year dog study, macroscopic dental fluorosis was not visible to the naked eye during the in-life phase or at necropsy at any dose level, including the high level of 200 ppm. However, histological examination of teeth revealed very slight or slight, microscopic concentric rings in the canine teeth that stained slightly darker and corresponded with each day of exposure at 80 and 200 ppm. As the teeth reached maturity it was more difficult to recognize the presence of the rings. These microscopic changes were not evident at 20 ppm.

In regard to the dental fluorosis in rats from the chronic toxicity/oncogenicity study (Quast et al., 1993), the Medical Toxicology Branch "Summary of Toxicology Data, Sulfuryl Fluoride" states that "Since the fluorosis is considered as a biomarker of exposure rather than as an adverse effect, a practical NOAEL is 20 ppm…" Also noted in the review is the fact that the U.S. EPA placed the NOEL at 20 ppm for this study. Dow AgroSciences agrees that 20 ppm is the appropriate value to consider for chronic exposure risk assessments.

In the 2-year rat study, macroscopic dental fluorosis was not visible to the naked eye during the in-life phase or at necropsy at any dose level, including the high-dose level of 80 ppm. After formalin fixation, repetitive pale and slightly darker colored horizontal lines became evident on the labial surface of incisor teeth at 80 ppm; this change was never visible at 20 ppm, even after fixation. Microscopic dental fluorosis was diagnosed at 20 and 80 ppm. The dental fluorosis of the incisor teeth of rats was detected microscopically as basophilic lines in dentin and enamel in the incisor teeth. There was no significant change in ameloblasts, odontoblasts or dental pulp. The microscopic changes in the incisors were not detected in the molars. These findings are consistent with the fact that only the incisor teeth of rats erupt continuously during life and are maintained at a constant length by attrition of the occlusal surfaces. Total renewal of rat incisors normally occurs approximately every 40 to 50 days. Therefore, during the course of the 24-month study the incisor teeth were renewed approximately 15 to 18 times without significant clinical dental problems in any group. Although several male rats (12%) in the 20 ppm group had very slight microscopic change in their teeth ('few, barely visible darker-stained concentric rings'), this effect is considered a biomarker of fluoride exposure in the rat and not an adverse effect.

Dental fluorosis of rodent incisor teeth is an inappropriate model for humans since rat incisor teeth continue to grow throughout adult life. Thus, fluoride-related dental changes in the continually erupting incisor teeth of rats on chronic toxicity studies are not relevant for human risk assessment.

Humans are not susceptible to dental fluorosis after 6-8 years of age (susceptibility is only during preeruptive development of teeth). Adult fumigation workers are not susceptible to dental fluorosis and thus, this end point is not relevant to chronic risk assessments. Although children ≤ 6-8 years of age could be considered for bystander and re-entry exposure assessments, these potential exposures are occasional (once every ~10 years) as well as transient (possibly minutes to hours for bystanders) or acute (1-2 days for re-entry). Furthermore, bystander and re-entry exposures are limited to very low levels of sulfuryl fluoride. Therefore, dental fluorosis is not a realistic possibility as a result of occasional, transient, low-level inhalation exposures to sulfuryl fluoride.

Low levels of fluoride intake are considered safe and health protective. In 1993 the National Research Council concluded that the EPA's Maximum Contaminant Level (MCL) of 4 mg/L for fluoride in drinking water continued to be appropriate as an interim standard. These governmental standards were set after extensive review of fluoride toxicological, medical, dental and epidemiological data that included consideration of infants and children as well as all sources of human fluoride exposure (World Health Organization, 1984; U.S. Public Health Service, 1991; National Research Council, 1993).

The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (DRI Committee, 1997) provides a consistent and coherent definition of requirements and reference intakes for all essential nutrients and food components. The DRI Committee established an Adequate Intake (AI) level for beneficial effects of fluoride.

The DRI Committee (1997) evaluated the relationship among dental caries experience, dental fluorosis index and the fluoride concentration in drinking water. The Committee concluded that:

"…reduction in the average number of dental caries per child was nearly maximal in communities having water fluoride concentrations close to 1.0 mg/liter. This is how 1.0 mg/liter became the "optimal" concentration. That is, it was associated with a high degree of protection against caries and a low prevalence of the milder forms of enamel fluorosis. The average dietary fluoride intake by children living in optimally fluoridated communities was (and remains) close to 0.05 mg/kg/day (range 0.02 to 0.10 mg/kg/day…)"

The value of 0.05 mg fluoride/kg body weight/day and appropriate reference weights for each age group were used by the DRI Committee to establish AI values (amount needed for prevention of dental caries) for fluoride. Thus, 0.05 mg/kg body weight/day is considered as adequate intake of fluoride for all age groups.

The DRI Committee regarded enamel fluorosis as a cosmetic effect on the teeth of children. Because the cosmetic effects of the milder forms of enamel fluorosis are not readily apparent, moderate enamel fluorosis was selected as the critical effect for susceptible age groups. Enamel fluorosis is a dose-response effect caused by fluoride ingestion during the preeruptive development of the teeth. The pre-eruptive maturation of teeth is completed by 8 years of age and the teeth are no longer susceptible to fluorosis. Thus, a fluoride intake of 0.10 mg/kg body weight/day was identified as a LOAEL for moderate enamel fluorosis in children from birth through the age of 8 years.

<u>References:</u>

National Research Council. 1993. Health Effects of Ingested Fluoride. National Academy Press, Washington, D.C.

U.S. Public Health Service. 1991. Review of Fluoride, Benefits and Risks. Department of Health and Human Services.

DRI Committee. 1997. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academy Press, Washington, D.C.

World Health Organization (1984). Environmental Health Criteria 36, Fluorine and Fluorides. World Health Organization, Geneva.

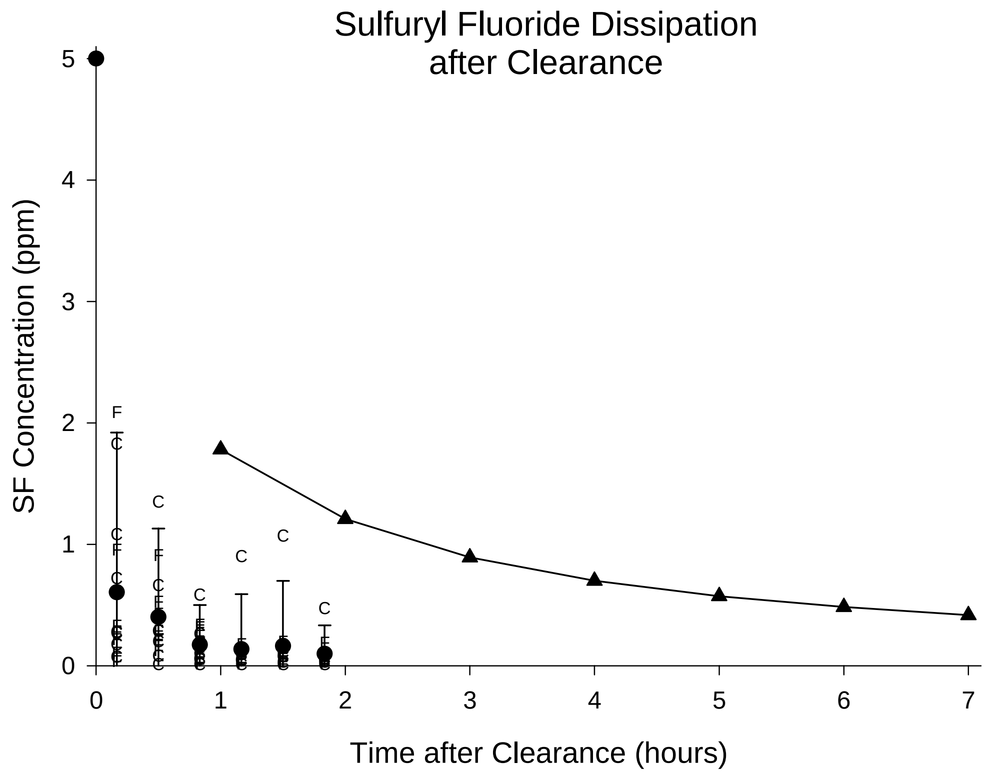
EXPOSURE ASSESSMENT

Calculations and Estimations of Residential Re-Entry Air Concentrations

The "best fit" mathematical function was not used to establish the post-clearance air concentration decay rate to calculate longer term re-entry exposure potential.

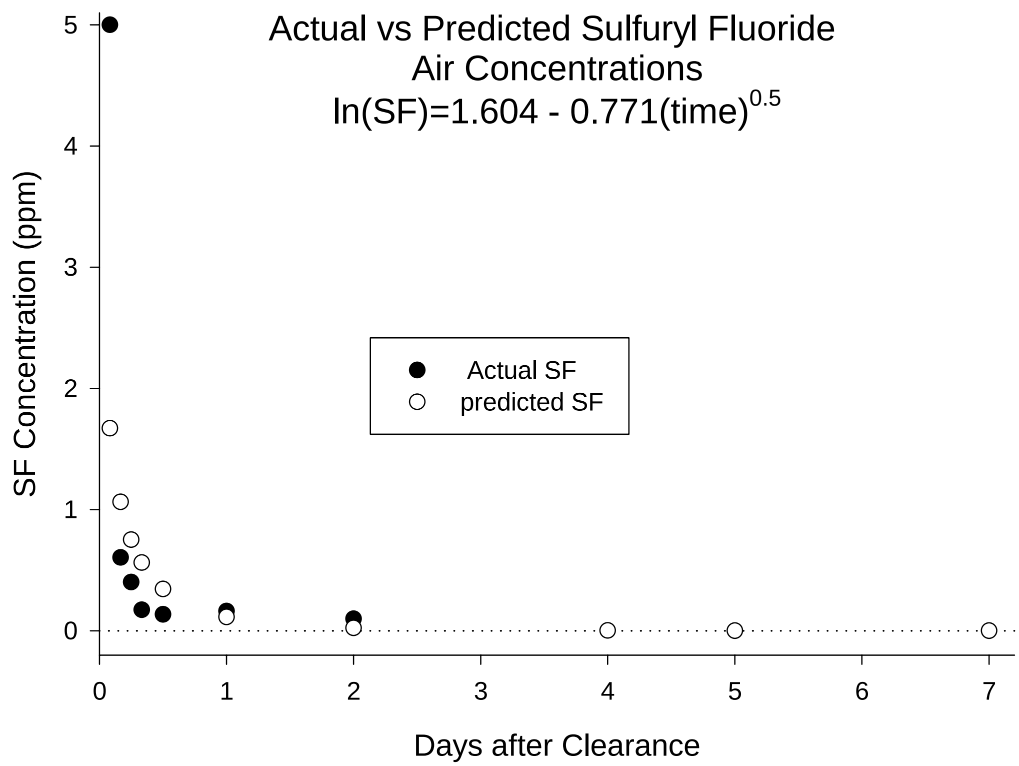
In establishing a model to estimate post-clearance air concentration decay rate to calculate longer term re-entry exposure potentials six models were evaluated. Three log-linear and three log-quadratic models were compared. Only small differences in R^2 were determined for like termed log-linear and three log-quadratic models indicating very little additional predictability by going to a log-quadratic function. On the other hand a significant increase in predictability was gained (increase in R^2) when additional terms, such as "House main effects", was added to the Hr term. Model 2 was identified as the best and simplest model that accounted for most of the variance that can be accounted for by any of the models evaluated. Therefore, model 2 should be utilized for estimate post-clearance air concentration decay rate to calculate longer term re-entry exposure potentials.

We do not understand several aspects of the exposure calculations as presented. In the calculations, the air concentrations presented in the Shurdut report are adjusted for a recovery factor of 64.6%. However, the data within the Shurdut report were already corrected by a method recovery of 90.6% and a field recovery spike of 64% as appropriate for the study. The study presented data from 14 houses fumigated in California and Florida. The data for all the sites are shown in the following Figure 1 and compared to the 95%tile air concentration values as calculated by CDPR. As can be seen, there appears to be no difference between the air dissipation rates for houses in California (C) vs. Florida (F). The error bars represent the upper 95%tile confidence limit calculated for the combined data at each time point. While differences in aeration procedures exist between California and Florida, there appears to be no quantifiable difference in the resultant dissipation of the SF from the fumigated homes. The aeration practices have no influence on the resulting dissipation once the building is cleared for re-entry. In the following analysis, the results from the California and Florida houses were combined.



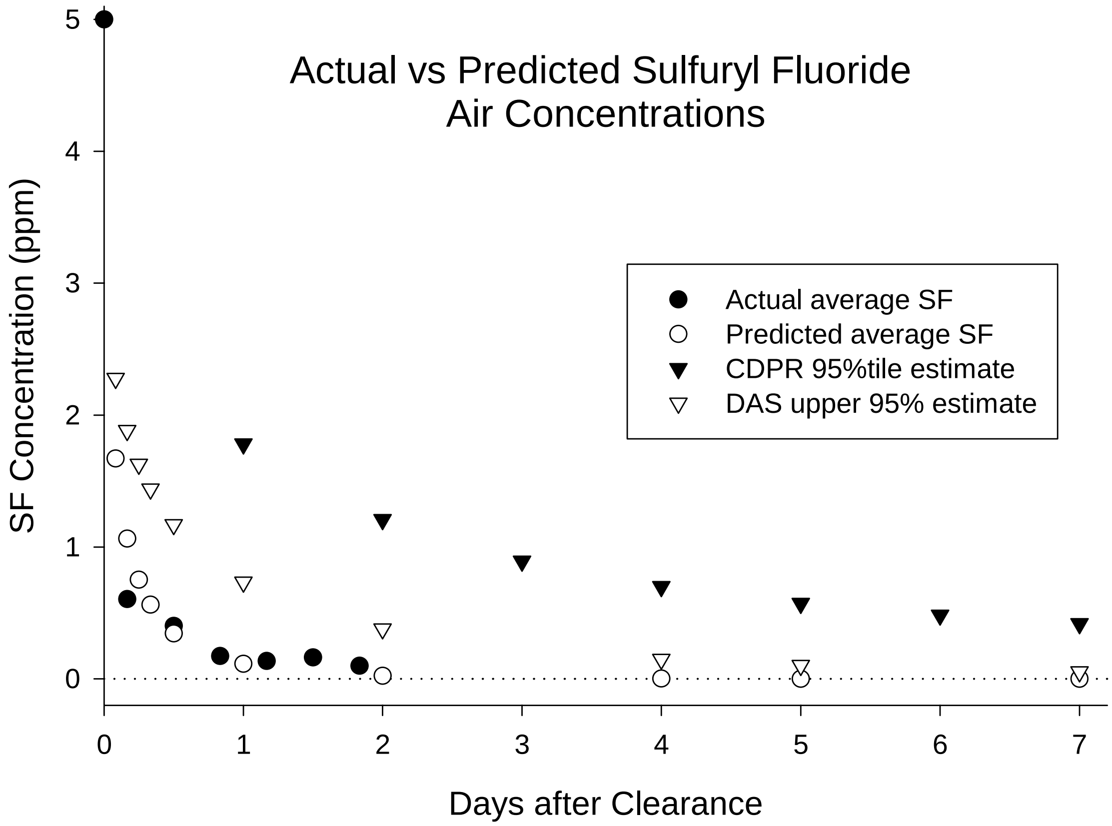
Measured vs. Predicted SF concentrations in treated houses after clearance to 5 ppm. Data from houses in California (C) and Florida (F) were combined. The house average data (•) plus 2 standard deviations (95%tile) are compared to the 95%tile, upper bound estimates used by CDPR (▲-▲).

The methods used to estimate the SF dissipation following clearance are not clear. The method as presented appears more complex than necessary and over-estimates the air concentrations. The data can be adequately modeled using the means at each time point as shown in the following figure except for the consistent over-estimation at times less than 1 day. The air concentration at time zero was assumed to be 5 ppm, the clearance value at the time of the study and most likely contributes to the discrepancy at times less than 1 day.



Actual vs. predicted air concentrations.

Of the many possible fits available in Table Curve 2D version 5.01, a reasonably simple form was chosen. As can be seen the equation given tends to over-estimate the air concentrations measured at less than 1 day but approaches zero much quicker than the CDPR estimates, and much closer to the data presented in the Shurdut report. Predictions of the upper 95%tile air concentrations were similarly obtained by fitting a curve to the individual, calculated upper 95% confidence limits for each measured time frame. This method better represents the confidence around the actual air measurements rather than the confidence around the fitted curve as presented by CDPR. A comparison of the two results is given in the figure and table below.



Comparison between the average measured vs predicted average air concentrations, and the upper 95% confidence limits calculated by DAS and CDPR.

Predicted air concentrations (ppm)

	SF (ppm)	
Days	Average *	Upper 95% **
0	5	ND***
0.25	0.75	1.63
0.5	0.34	1.71
1	0.11382	0.73
2	0.02381	0.38
4	0.00261	0.15
5	0.00107	0.10
6	0.00048	0.07
7	0.00023	0.05

* Mean SF air concentration calculated by: $\ln(SF) = 1.6\text{-}4 - 0.77\ (time)^{0.5}$
** Upper 95% air concentration calculated by: $\ln(SF) = 1.283 - 0.325\ (time)^{0.5}$
*** The air concentration at time zero was defined as 5 ppm, the clearance value

A comparison between the values calculated by CDPR (Appendix A. Tables 11 and 12) and DAS is provided below:

Air concentrations, integrated over time, for residences following clearance of homes to 5 ppm SF, CDPR vs DAS estimates.

Post Clearance Interval (days)	CDPR average	DAS average *	CDPR Upper 95% tile	DAS Upper 95%tile *
0-1	0.436	0.419	1.781	1.13
0-2	0.298	0.237	1.208	0.83
0-3	0.216	0.163	0.893	0.65
0-4	0.166	0.123	0.700	0.53
0-5	0.133	0.099	0.573	0.452
0-6	0.111	0.082	0.484	0.392
0-7	0.095	0.07	0.418	0.34

* calculated as the area under the curve at each time point (Table 1) divided by the number of days.

According to the published CDPR policy[1], upper confidence limits should only be used for short term assessments, i.e., exposures of less than 7 days duration. Using these values over- estimates potential exposures because they fail to incorporate activity levels and varying amounts of time spent in the home. A more appropriate method is to amortize the exposures based on time weighted averages with adjustment for the amount of time actually spent in the home.

Selection of Proper Indicator of Central Tendency

Because the exposure monitoring results are typically skewed log-normally based on a statistical test for normality, the appropriate central tendency statistic should be the geometric mean. Further, when examining a large number of repeated measurements of individual and between individual exposures to pesticides, it is clear that intra-individual variability is greater than inter-individual variability so that the population mean is a more meaningful indicator of an individual's average daily exposure than any given daily measurement (Kromhout and Vermeulen, 2001).

US EPA's Scientific Advisory Panel summarized the conclusion well with the following quote. "When inflated "central tendency" values are put into the deterministic exposure calculation, they can be expected

[1] Memo. October 4, 2001. Chuck Andrews, Chief, Worker Health and Safety Branch to Gary Patterson, Chief, Medical Toxicology Branch. WORKER HEALTH AND SAFETY BRANCH POLICY ON THE ESTIMATION OF SHORT-TERM, INTERMEDIATE-TERM, ANNUAL AND LIFETIME EXPOSURES. HSM-01014.

to overestimate the expected or "central tendency" exposure. If the distribution of exposure is highly positively skewed, this bias may be considerable. In some cases the arithmetic mean values are substantially skewed and should be replaced by median values as a better indicator of central tendency. Working with high end values will be even worse, as the result will correspond to the very rare event of an exposure that is extreme in every respect and hence will be higher than is ever observed in reality." (FIFRA SAP December 12, 2001).

ACGIH is quoted in the Introduction to the Chemical Substances TLVs:

> "The approach here is that the maximum recommended excursion should be related to the variability generally observed in actual industrial processes. In reviewing large numbers of industrial hygiene surveys conducted by the U.S. National Institute for Occupational Safety and Health, Leidel et al. (1975) found that short-term exposure measurements were generally lognormally distributed.
>
> While a complete discussion of the theory and properties of the lognormal distribution is beyond the scope of this section, a brief description of some important terms is presented. The measure of central tendency in a lognormal distribution is the antilog of the mean logarithm of the sample values. The distribution is skewed, and the geometric mean (m_g) is always smaller than the arithmetic mean by an amount that depends on the geometric standard deviation. In the lognormal distribution, the geometric standard deviation (sd_g) is the antilog of the standard deviation of the sample value logarithms, and 68.26% of all values lie between m_g/sd_g and $m_g \times sd_g$.
>
> If the short-term exposure values in a given situation have a geometric standard deviation of 2.0, 5% of all values will exceed 3.13 times the geometric mean. If a process displays variability greater than this, it is not under good control, and efforts should be made to restore control."

US EPA (1992):

> "Exposure and dose profiles often fall in a skewed distribution that many times appears to be approximately lognormally distributed, although statistical tests for lognormality may fail. The arithmetic mean and the median are the same in a normal distribution, but exposure data are rarely normally distributed. As the typical skewness in the distribution increases, the exposure or dose distribution comes to resemble a lognormal curve where the arithmetic mean will be higher than the median. It is not unusual for the arithmetic mean to be located at the 75th percentile of the distribution or higher. Thus, the arithmetic mean is not necessarily a good indicator of the midpoint (median, 50th percentile) of a distribution.
>
> The average estimate, used to describe the arithmetic mean, can be approximated by using average values for all the factors making up the exposure or dose equation. It does not necessarily represent a particular individual on the distribution, but will fall within the range of the actual distribution.

Historically, this calculation has been referred to as the average case, but as with other *ad hoc* descriptors, definitions have varied widely in individual assessments.

When the data are highly skewed, it is sometimes instructive to approximate the median exposure or dose, or median estimate. This is usually done by calculating the geometric mean of the exposure or dose distribution, and historically this has often been referred to as the typical case, although again, definitions have varied widely. Both the average estimate and median estimate are measures of the central tendency of the exposure or dose distribution, but they must be clearly differentiated when presenting the results."

"Exposure assessments should take into account the time scale related to the biological response studied unless the assessment is intended to provide data on the range of biological responses (NRC, 1990, p. 28). For many noncancer effects, risk assessments consider the period of time over which the exposure occurred, and often, if there are no excursions in exposure that would lead to acute effects, average exposures or doses over the period of exposure are sufficient for the assessment. These averages are often in the form of average daily doses (ADDs). An ADD can be calculated from Equation 2-2 by averaging D_{pot} over body weight and an averaging time, provided the dosing pattern is known so the integral can be solved. It is unusual to have such data for human exposure and intake over extended periods of time, so some simplifying assumptions are commonly used. Using Equation 2-4 instead of 2-2 or 2-3 involves making steady-state assumptions about C and IR, but this makes the equation for ADD easier to solve.   For intake processes, then, using Equation 2-4, this becomes:

$$ADD_{pot} = [\,\bar{C} \cdot \bar{IR} \cdot ED\,] \;/\; [BW \cdot AT]$$

Where ADD_{pot} is the average daily potential dose, BW is body weight, and AT is the time period over which the dose is averaged (converted to days). Concentration is best expressed as an estimate of the arithmetic mean regardless of the distribution of the data."

RISK CHARACTERIZATION

Temporal Matching of Toxicological Endpoint and Exposure Period

A key to credibility and meaningfulness of any risk assessment is the appropriate pairing of exposure duration with toxicity study duration or observed time to effect (Ross et al., 2001). The SF RCD is particularly weak in this area. The Haber Principle indicates that for many compounds, longer exposure results in lower NOAELs. This is not always true, however (Cochran and Ross, 2003), and it does not appear to be true for SF in particular. If one examines LOAEL for neurotoxicity (Table 15 of the RCD), it is remarkably stable over short to long durations of exposure. There appears to be several causes for the mismatches of exposure duration and toxicity study duration in the SF assessment. The primary cause appears to be policy differences between the Medical Toxicology Branch and the Worker Health and Safety Branch and perhaps a failure to communicate the need for chemical-specific exposure durations. This is alluded to in the RCD on page 55 "Since the exposure durations in the toxicology studies are defined differently than some of the scenarios in the Exposure Assessment (Appendix C), the applicable NOELs for the exposure durations are presented in Table 23." With the rapid dissipation rate of a gas, the exposure duration can have a dramatic effect on the absorbed dosage.

The example of short-term exposure is a particularly pertinent mismatch. Worker Health and Safety derived an estimate of short term exposure based on 1-7 days of exposure, while Medical Toxicology used an endpoint from the two-week rabbit inhalation study. Thus, while Worker Health and Safety provided a 95 percentile upper bound estimated exposure for one week of exposure, Medical Toxicology calculated MOE from a two-week duration rabbit toxicity study. The net effect is not significant for workers, but for residential exposures, the differences are large. For example, air levels reentering a treated structure fall to zero before day 7 and if exposure were averaged over 2 weeks rather than 1 week, MOEs would more than double and consistently exceed 100.

Another example of mismatch of exposure duration and toxicity study duration occurred in the interpretation of the acute neurotoxicity study in which rats were exposed 12 hours (2x6 hr) in a 30 hour period of time. Medical Toxicology calculated the dosage on a 24 hour basis (functionally lowering the NOEL by 22%). Worker Health and Safety derived a 95th percentile estimate of exposure for 0-1 or 0-2 days. If exposure had been estimated at 0-1.25 days (i.e., the 30 hour duration of the toxicity study), and compared to the NOAEL over the same period of time, MOE would again consistently exceed 100. The lack of congruity between the toxicology study duration and human exposure duration suggests there may be poor communication between branches.

There is no subchronic, or chronic/lifetime exposure to residents from structural fumigation with Vikane for several reasons. First, structural fumigation is costly (typically ≥$2,000) and disruptive if the structure is inhabited because it displaces a family from their residence for several days. Secondly, homes are most frequently fumigated as a condition of real estate sale (they are uninhabited at the time fumigation is required). Thirdly, a re-infestation of dry wood termites requires approximately 4 years to achieve a “critical mass” when visible damage might be observed. Finally, the exposure estimates derived for these endpoints are not credible because they amortize 1-7 days of exposure over durations that are orders of magnitude larger. Given that many of the toxic effects experienced from acute or short term exposure to SF below the LOAEL are reversible, there is no carryover of effect from doses spaced years apart.

UNCERTAINTY

Using the 95th percentile for acute and short term exposure appears to be policy, but the scientific basis for the policy (which increases the acute and short term exposures approximately 4-fold over a central tendency value) appears to be neither stated nor referenced. The upper bound estimate of acute exposure is particularly onerous because it is purely theoretical. A structure might be inhabited immediately after it was cleared for occupancy, but this is an extremely rare occurrence. The practice of calculating an upper bound (with low probability) exposure on a low probability event is troubling. A resident is typically not allowed to reoccupy their homes for 12 hours after the structure is cleared i.e., the morning after it was cleared. Most of the fumigated houses were not occupied immediately prior to fumigation with little prospect of immediate occupancy after the fumigation because they were involved in a real estate transaction. Thus, DPR has calculated acute exposure on the basis of 3 concurrent low probability events. This practice goes beyond “health protective”, but that was not communicated to risk managers.

Because the RCD will be the basis of any subsequent risk mitigation, it is imperative that the risk manager be honestly apprised of the degree of conservatism inherent in this particular RCD. The RCD risk appraisal section provides some qualitative indications of the degree of conservatism, but makes no attempt to quantify it. There is a large amount of conservatism built into both the hazard identification/dose response (NOEL) portion as well as the exposure portion of the RCD on SF. Exposures tend to be overestimated and the NOELs tend to be underestimated, thus resulting in a multiplicative conservative bias far beyond the 100-fold uncertainty that is acknowledged.

On the hazard identification side, we have already discussed the bias in the interpretation of NOELs. In most instances, Dow AgroSciences agrees with the choice of study in characterizing hazard for that exposure duration, but disagrees with interpretation of the absorbed dose in that toxicity study. Dow AgroSciences frequently agrees with the concentration of SF chosen as NOEL, but does not agree on how that concentration is transformed into dosage. In most cases, CDPR appears to have erred on the conservative side, but there are exceptions. To briefly summarize, Dow AgroSciences believes that the acute toxicity endpoint NOEL from Albee et al., 1993 is underestimated by 22%. This is because CDPR is interpreting this study as though dosing was in 24 hour intervals, when in fact the exposure terminated at 30 hours, and neurotoxicity effects-testing began immediately thereafter. Thus the averaging time is 1.25 days and not 1 or 2 days. For the chronic endpoint (which should be based on the lifetime inhalation study in rats, and not the subchronic rat reproductive toxicity study), if the chronic study endpoint used was nephrotoxicity the NOEL would increase four-fold. Detailed explanations of these interpretive issues are provided in other parts of this document. The differences in estimation of NOAEL dosages between CDPR and Dow AgroSciences are summarized in the Table below.

Summary of Underestimated NOAELs Derived by CDPR for Vikane			
Variable	**CDPR**[a]	**Realistic**[b]	**Underestimate**[c]
Acute dosage	300 mg/kg/day	384 mg/kg/day	22%
Chronic dosage	4 mg/kg/day	16 mg/kg/day	4

[a] Dosages used in CDPR's final draft RCD assessment
[b] Dosages more consistent with the data
[c] Underestimate of dosage compared to CDPR's estimates (negative numbers signify overestimate)

On the exposure side, there are several quantifiable overestimates that have been used by CDPR. For the acute and short term exposures, it is not clear why CDPR used the 95th percentile exposures rather than an estimate of central tendency. Using the 95th percentile for acute and short term exposure appears to be policy, but the scientific basis for the policy (which increases the acute and short term exposures approximately 4-fold over a central tendency value) appears to be neither stated nor referenced. The upper bound estimate of acute exposure is particularly onerous because it is purely theoretical. A structure might be inhabited immediately after it was cleared for occupancy, but this is an extremely rare occurrence. The practice of calculating an upper bound (with low probability) exposure on a low probability event is troubling. A resident is typically not allowed to reoccupy their homes for 12 hours after the structure is cleared i.e., the morning after it was cleared. Most of the fumigated houses were not occupied immediately prior to fumigation with little prospect of immediate occupancy after the fumigation because they were involved in a real estate transaction. Thus, DPR has calculated acute exposure on the basis of 3 concurrent low probability events, i.e., the actual exposure calculated is closer to the 99.9th percentile. This practice goes beyond "health protective", but that was not communicated to risk managers. Additional overestimates (20-30%) occurred because the Florida-fumigated houses were excluded from estimates of residual air levels, although these homes had been cleared to the same levels as California houses. Further, the short term exposures are calculated for a maximum of 7 days and not for the duration of the 14-day rabbit toxicity study thereby overestimating exposure at least 2-fold. Additionally, CDPR has traditionally used a central tendency estimate for multi-day exposures and no reason was given for deviating from the method traditionally used (and the method used by other regulatory agencies throughout the world). Other obvious overestimates resulted from assuming a 40-year SF handler career, when 2 independent epidemiology studies cited in the RCD clearly indicated the average career span for SF handlers was 3-7 years (Anger, 1986; Calvert et al., 1998). The assumption that workers are involved in fumigation 49 weeks per year is very difficult to support. Whether due to sick leave, vacation, weather prohibitions, work activities not involving fumigation, or equipment shortages, it is extremely unlikely an employee will handle SF 49 weeks per year. Finally, the exposure frequency (number of days per week) was not used to calculate short or intermediate term worker exposure, although such a correction was used to calculating the animal NOEL. This results in approximately a 2-fold overestimation of exposure. A summary of the major discrepancies are summarized in the following table.

Partial Summary of Conservative Factors Applied to Estimated Exposures Derived by CDPR for Vikane			
Variable	**CDPR**[a]	**Realistic**[b]	**Overestimate**[c]
Resident Post Clear, acute	95^{th} percentile	mean	4
Resident Post Clear, subacute	7-day, 95^{th} %tile	14-day avg	>8
Resident Post Clear	Exclude FL data	Include FL	1.25
Resident/Bystander chronic	Annual fumigate	>10 yr cycle	>10
Use frequency (days per week)	7/7 Short/Interm.	3.7/7 to 4/7	1.8 to 1.9
Body Weight (worker)	70 kg	85 kg	1.2
Vikane Handler freq	49 wk/yr	48 wk/yr	1.02
Vikane Handler duration	40 years	10	4

[a] Exposure defaults used in CDPR's final draft RCD assessment
[b] Exposure factors more consistent with "normal"
[c] Overestimate of exposure compared to Dow AgroSciences' estimates

CALCULATION OF MARGINS OF EXPOSURE (MOE)

The calculations of MOEs within the RCD include the questionable use and interpretation of the available sulfuryl fluoride toxicology and exposure data. In addition, unnecessarily conservative assumptions regarding the calculation of exposure, and in turn risk, are included in the RCD. To fully, and accurately use the information available to support the evaluation of sulfuryl fluoride, and to establish a more realistically conservative evaluation of human, inhalation risk for the various subpopulations that can encounter exposures to sulfuryl fluoride (Vikane), the following refined MOE are calculated and presented. For each subpopulation, the MOE (or range of MOEs) calculated within the RCD are refined by correcting misinterpretations of the data, or by substituting a more realistic data set or interpretation of the data These adjustments are described as "Adjustment Factors" (AF) and are described sequentially. Several other adjustments could be made (see Uncertainty section). The combination of the AFs for each of the subpopulations is utilized to calculate the final MOEs for the DWT scenarios. Although not summarized here, the same AF would be useful to recalculate human inhalation exposure potential in the PPB scenarios. The range of the refined MOEs (245 to 2,807 for workers and 357 to 15,161 for residential subpopulations) using realistically conservative exposure assumptions and appropriate interpretations of the SF toxicological data all satisfy the minimum regulatory target of 100. The MOEs calculated and described within this document support the perspective of Vikane uses in the State of California as representing acceptable human inhalation exposure and risk potential when handled in conformance with product label directions and local regulations.

Occupational Exposure and Risk

Fumigator Worker (Total Activities) - Acute	
RCD Calculated MOE	**1,432**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Air concentration input for calculation (95th Percentile "Shift-TWA" measured vs. 95th Percentile calculated)	AF = 2.48x
Final, Adjusted MOE	**6,712**

Tent Crew Workers (Total Activities) - Acute	
RCD Calculated MOE	**48**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Air concentration input for calculation (95th Percentile "Shift-TWA" measured vs. 95th Percentile calculated)	AF = 17.7x
Final, Adjusted MOE	**1,606**

Fumigator Worker (Total Activities) – Short-Term	
RCD Calculated MOE	**191**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. 95th Percentile calculated)	AF = 44.1x
Final, Adjusted MOE	**15,161**

Tent Crew Workers (Total Activities) – Short-Term	
RCD Calculated MOE	**6**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. 95th Percentile calculated)	AF = 103.4x
Final, Adjusted MOE	**1,117**

Fumigator Worker (Total Activities) – Intermediate/Annual	
RCD Calculated MOE	**111**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 13.2x
Final, Adjusted MOE	**2,637**

Tent Crew Workers (Total Activities) – Intermediate/Annual	
RCD Calculated MOE	**8**
Appropriate conversion of daily exposure to reflect days exposed per week.	AF = 1.8x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 24.8x
Final, Adjusted MOE	**357**

Fumigator Worker (Total Activities) – Lifetime	
RCD Calculated MOE	**67**
Appropriate Chronic NOEL for systemic effects relevant to humans (20 ppm vs. 5 ppm in RCD)	AF = 4.0x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 13.2
Worker duration assumption (nominal career length is 10 years for these workers rather than 40)	AF = 4.0x
Final, Adjusted MOE	**14,150**

Tent Crew Workers (Total Activities) – Lifetime	
RCD Calculated MOE	**5**
Appropriate Chronic NOEL for systemic effects relevant to humans (20 ppm vs. 5 ppm in RCD)	AF = 4.0x
Air concentration input for calculation (geometric mean of measured "Shift-TWA" values vs. arithmetic mean of calculated values)	AF = 24.8x
Worker duration assumption (nominal career length is 10 years for these workers rather than 40)	AF = 4.0x
Final, Adjusted MOE	**1,984**

Residential Exposure and Risk

Residential Re-Entry Exposure Following Clearance – Acute	
RCD Calculated MOE	**115 to 270**[1]
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
Air concentration input for calculation (Dow AgroSciences calculated 95th percentile value of 1.13 ppm vs. RCD 95th percentile value of 1.78 ppm)	AF = 1.57x
Final, Adjusted MOE	**341 to 801**

[1] The described range is derived from the calculated MOEs for the various age groups within this subpopulation

Residential Bystander Exposure During Fumigation – Acute	
RCD Calculated MOE	**113 to 270**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
95th Percentile Air Concentration for 24 hr TWA(0.97 ppm vs. 1.12 ppm)	AF = 1.15x
Final, Adjusted MOE	**245 to 587**

Residential Bystander Exposure During Aeration (TRAP) – Acute	
RCD Calculated MOE	**72 to 150**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
95th Percentile Air Concentration for 24 hr TWA(5 ppm vs. 24 ppm)	AF = 4.8x
Final, Adjusted MOE	**653 to 1,361**

Residential Bystander Exposure During Aeration (STACK) – Acute	
RCD Calculated MOE	**450 to 900**
Appropriate conversion of acute NOEL (567 mg/kg/day vs. 300 mg/kg/day)	AF = 1.89x
95th Percentile Air Concentration for 24 hr TWA(1.19 ppm vs. 1.97 ppm)	1.65x
Final, Adjusted MOE	**1,403 to 2,807**

Mary-Ann Warmerdam
Director

MEMORANDUM

Arnold Schwarzenegger
Governor

TO: Gary Patterson, Ph.D.
Supervising Toxicologist
Medical Toxicology Branch

VIA: Keith Pfeifer, Ph.D., D.A.B.T. *[original signed by Keith Pfeifer]*
Senior Toxicologist
Medical Toxicology Branch

FROM: Lori O. Lim, Ph.D., D.A.B.T. *[original signed by Lori Lim]*

Staff Toxicologist
(916) 324-3515

DATE: May 10, 2005

SUBJECT: RESPONSES TO COMMENTS FROM DOW AGROSCIENCES ON DRAFT SULFURYL FLUORIDE RISK CHARACTERIZATION DOCUMENT FOR AB 1807 THE AIR TOXIC CONTAMINANT ACT

This memorandum addresses toxicology and risk characterization related comments on the draft Risk Characterization Document (RCD) (August 26, 2004) submitted by Dow AgroSciences (DAS, SBRA 209121) as part of the AB 1807, The Air Toxic Contaminant Act, public review process. Some of the comments were the same as those submitted by DAS (July 12, 2004; Dow AgroSciences, 2004) for the Department's draft document dated March 16, 2004 as part of the SB 950 review process.

Comment I. Page 10 under Toxic Air Contaminant Considerations, DAS questioned whether air at a work site is ambient air, and commented that a specific ambient air concentration for regulatory purposes was not identified.

Response: First, DPR has used application site air concentration as the acute ambient air concentration for AB 1807 evaluation of pesticides; for example, methyl parathion and metam sodium. Regional air monitoring data are used for subchronic and chronic exposures. Second, the RCD clearly indicated that the acute reference concentration for infants was the specific ambient air concentration for regulatory purpose. This reference concentration was used to evaluate the estimated human exposures.

Comment II. Pages 10 to 17 under Occupational Exposure. DAS concluded that the two studies of methyl bromide and sulfuryl fluoride fumigation workers in California (Anger et al., 1986) and Florida (Calvert et al., 1998) did not demonstrate adverse health effects.

Response: The summaries of these two studies in the RCD reflected what was stated in the reports. As pointed out in both the RCD and DAS in their submitted comments, these studies had limitations and confounding factors. Therefore, definitive statement could not be made as to whether sulfuryl fluoride caused the effects discussed in the papers.

Comment III. Pages 17-18 under Selection of Endpoints. DAS commented that the RCD should include additional comments on the significance of fluoride in regard to sulfuryl fluoride toxicity. DAS considered fluoride as the toxic metabolite for all toxicological endpoints after sulfuryl fluoride exposure. DAS cited a mouse study where there were increased serum fluoride and cerebrum vacuolation. Eisenbrandt and Nitschke (1989) was cited as a publication which discussed the similarities between sulfuryl fluoride toxicity and fluoride toxicity.

Pages 24-26 under Mammalian Pharmacokinetics and Metabolism (ADME), DAS commented that pharmacokinetic study showed a lack of systemic exposure to sulfuryl fluoride and that the systemic toxicity was attributed to fluoride.

Response: The revised RCD will expand the discussion on the propose role of fluoride in the systemic toxicity of sulfuryl fluoride. DPR considered the data adequate to demonstrate such a role for dental fluorosis, but only a reasonable assumption for the other endpoints. The revised RCD will provide analysis of data from sodium fluoride and sulfuryl fluoride chronic toxicity. It will also include a comparison of serum fluoride levels and vacuolation incidences in the 13-week sulfuryl fluoride toxicity studies.

Comment IV. Page 19 under Selection of No-Observed-Effect Levels: Acute Toxicity. While DAS agreed with DPR on the selection of the study and NOEL (300 ppm) for acute exposure, DAS disagreed with the DPR calculation of the daily dose.

Response: DPR recognizes that the 2-day acute neurotoxicity study protocol (Albee *et al*., 1993a and b) was specifically designed to determine the toxicity following reentry and was approved by the U.S. EPA to meet the acute neurotoxicity study requirement. Since no effects were observed at 300 ppm, the highest dose tested, the U.S. EPA concluded that this exposure scenario was not of concern. At the same time, the U.S. EPA did not evaluate single day exposure because a toxicity endpoint from a single exposure was not available.

In comparison, DPR is concerned about acute exposures, especially to peak concentration, of workers and bystanders, and residents on the first day of reentry. It is unfortunate that the two-day study did not include any observations for the first day and the highest dose did not show any effects. Lacking the standard 1-day acute neurotoxicity study, DPR chose to use the results from this two-day study because it is more comprehensive than other acute studies. As explained in the RCD under the Risk Appraisal section, this NOEL of 300 ppm when expressed in terms of dosage (300 mg/kg/day) is supported by data from other acute exposure studies. Lethargy was observed at 500 mg/kg/day (750 ppm after 4 hours) and death at 600 mg/kg/day (600 ppm after 6 hours between the 2^{nd} and 6^{th} dose) in rats (Table 3 in the RCD). These values are lower than the DAS proposed acute NOEL of 567 mg/kg/day extrapolated from the 300 ppm NOEL. In other words, the use of 567 mg/kg/day as the acute NOEL would not be protective because at a slightly higher dose of 600 mg/kg/day caused death in rats. Furthermore, the current sulfuryl fluoride label does not restrict human exposure to 30-hours with 18-hours of no exposure between daily exposures as designed in this study. An adjusted NOEL using this fixed exposure scheme would have limited uses. Therefore, the critical acute NOEL should remain at 300 ppm or 300 mg/kg/day.

Comment V. Page 22 under Calculations from No-Observed Effect Levels (NOEL), DAS commented that the RCD was inconsistent in normalizing animal exposure vs. human exposure...If normalization is needed in the conversion of animal NOELs to human NOELs for short term, subchronic and chronic potential exposures then the two terms used in the conversion of the NOELs must be accounted for in the calculation of exposure estimates."

Response: Since the exposures in the toxicity studies and those for humans are usually not the same, there is no accurate method to match the duration of these exposures. In the RCD, the NOELs as ppm air concentration were amortized to daily exposure dosage (mg/kg/day) for all exposure durations. As discussed in response to other comments, there is uncertainty related to this approach, which may result in the over- or under-estimation of the risk depending on the exposure scenario. DPR will review any additional toxicology studies, which may better characterize the risk.

Comment VI. Page 24 under Calculation of Reference Concentration, DAS commented that "...the calculation of the reference concentration using a child-specific respiration rate is not applicable to durations of exposure that do not exist for the child..."

Response: The RCD provided RfCs for both children and adults for acute and repeated exposures. But only the infant acute RfC was used in the comparison with exposures. Other values in this RCD may be used in future evaluation of sulfuryl fluoride as ProFume®.

Comment VII. Page 25. "The estimated absorbed dose was 14.1% or 12.4%, respectively, for exposure concentration of 30 ppm and 300 ppm. However, internal dose calculations for purpose of risk assessment were based on the default of 100% absorption.

Response: In the March version of the RCD, a default 100% absorption factor was used in estimating the human exposures because the pharmacokinetic study was not available to DPR at that time. However, in the August draft RCD, DPR revised the NOELs and exposures using 18% as the absorption factor based on DPR determination of the absorption factor.

Comment VIII. Page 26, first paragraph, under Selection of No-Observed Effect Levels for Chronic Toxicity. DAS commented on the DPR daily dosage calculation for the reproductive toxicity study based on a 5 days/week exposure instead of 7 days/week. In contrast, DAS suggested that it should be based on 7 days/week.

Response: In the reproductive toxicity study (Breslin *et al*., 1992), the protocol described in the report is indicated in the following table. As shown in the table below, the rats were exposed 5 days/week during premating (for 10 weeks for F0 and 12 weeks for F1, excluding holidays), and 7 days/week during mating (1 to 3 weeks), gestation (3 weeks), and lactation (3 weeks). The exposure during gestation and lactation (to postpartum day 21) was not continuous because females were not exposed to sulfuryl fluoride from gestation day 21 to postpartum day 4 (about 10 days). For the F0 generation, the total duration was about 20 weeks and approximated a subchronic exposure-type scenario. For the F1 generation, the total duration was longer with *in utero,* lactation, premating, mating, gestation, and lactation periods of exposures. While the total was about 25 to 27 weeks, it is not appropriate to simply add up the weeks of exposure for the F1 generation. These periods of exposures for this generation expand from fetus to adulthood with days of no exposures in between. Therefore, the F1 exposure should be considered a chronic exposure scenario.

Week	**F0**	**F1**
1-10	Premating at 6 weeks old Exposed 6 hrs/day, 5 days/week (excluding holidays)	
11	Mating/gestation/lactation Exposed 6 hrs/day, 7 days/week, to postpartum day 21, except no exposure for females from gestation day 21 to postpartum day 4. Exposure during mating was 1 to 3 weeks.	
12		
13		
14		Fetus/Pup exposure: -In utero up to gestation day 20 to birth -Via milk from birth to postpartum day 21. -No exposure from 3 to 6 weeks old (after weaning)
15		
16		
17		
18		
19		
20-31	Sacrifice on week 20	Premating (assume at 6 weeks old) Exposed 6 hrs/day, 5 days/week (excluding holidays)
32-41		Mating/gestation/lactation Exposed 6 hrs/day, 7 days/week, to postpartum day 21, except no exposure for females from gestation day 21 to postpartum day 4. Exposure during mating was 1 to 3 weeks.

As for the calculation of a daily dosage, DPR calculated the dosage (4 mg/kg/day) for the NOEL (5 ppm) based on the continuous exposure period, which was during premating at 5 days per week. This approach also took into consideration days of no exposure during the periods of 7 days per week of exposure. In comparison, the dosage calculation performed by DAS assumed that the effects observed were due to repeated daily exposure during the entire study. Since daily exposure occurred only during parts of the study, this assumption results in an overestimation of the NOEL (6 mg/kg/day). Therefore, calculated dosage of 4 mg/kg/day for this study in the draft RCD remained the more appropriate value.

Comment IX. Page 26, second paragraph, under Selection of No-Observed Effect Levels for Chronic Toxicity, DAS commented that "increase in alveolar macrophages is a manifestation of the irritancy properties of sulfuryl fluoride to the respiratory tract which is a portal of entry effect rather than a systemic effect. In contrast to the increase in alveolar macrophages in the lungs of rats exposed to 20 ppm for 7 days/week for 4-5 months on the reproduction study, lungs of rats, mice or dogs exposed to 20 ppm sulfuryl fluoride 5 days/week for 12, 18 or 24 months did not have alveolar histiocytosis or other effects. Since 5 days/week exposure was closely approximates the potential human exposure for workers, the NOEL of 20 ppm from the chronic studies with rats or dogs is more appropriate for repeated-exposure risk assessment."

<u>Response</u>: There are three issues raised with this comment: (1) use of portal of entry effect and systemic effect for risk characterization, (2) exposures between 5 days/week and 7 days/week, and (3) comparison of NOEL based on air concentrations.

The DAS comment implied that irritation should not be used as a critical endpoint for risk characterization. At the meeting with DPR (June 15, 2004), DAS indicated that the irritation occurred at the nasal passages and was due to fluoride ions. DPR disagrees with the DAS position. First, pulmonary irritation should be considered an adverse effect because it can have severe consequences for people with certain health conditions such as asthma. Second, the lung effects reflected tissue injury and may not be due to nasal irritation alone. The data from the two-generation reproductive toxicity study (Breslin *et al*., 1992) showed that alveolar macrophage aggregates were found beyond the nasal passages in the subpleural and peribronchial locations. These lesions were frequently accompanied by chronic inflammation in the high dose group. As noted in the following paragraph from the study (pages 24-25 of the study report), the effects were considered evidence of lung injury by the study authors:

"The pathogenesis of spontaneously occurring aggregates of alveolar macrophages is unknown, but the incidence increases with age in untreated rats (Anver and Cohen, 1979) and was observed in control rats in this study. However, a common response to lung injury is an increase in these macrophages. With significant, repeated injury, multifocal lesions of the alveolar wall, with inflammatory cells, type II pneumocytes and alveolar fibrosis may be seen in addition to the luminal macrophages (Haschek and Witschi, 1991). This was the pathologic picture observed in many of the rats exposed to 150 ppm in which observations of "aggregates of alveolar macrophages" and "inflammation, chronic" were made."

The second part of the comment implied that the effect was due to continuous daily exposure (in the rat reproductive toxicity study) and pulmonary effects were not observed when animals were observed for 5 days per week exposure. As shown in the response to **Comment VIII**, the dosing regimen in the reproductive toxicity study included both 5 days per week and 7 days per week regimen, plus some non-exposure days.

Third, DPR disagrees with DAS approach of comparing NOELs based only on air concentration. DPR adjusts the NOELs with animal breathing rates to account for differences in the uptake between experimental animals. As shown in the RCD, lung inflammation and alveolar macrophage aggregates were observed in dogs with a similar NOEL in terms of dosage (6 mg/kg/day) (Quast *et al*., 1993) as that for the rat reproductive toxicity study (4 mg/kg/day).

Comment X. Pages 26 to 28, DAS commented that dental fluorosis should not be considered an endpoint.

<u>Response</u>: With regard to dental fluorosis, the RCD did not base the risk estimation on this endpoint because other endpoints had lower NOELs. Dental fluorosis was not reported for acute exposure. Brain lesion was the most sensitive endpoint for 1-2 weeks, and subchronic exposures. The draft RCD clearly stated that the risk assessment considered respiratory system effects as the critical effect for chronic inhalation exposure.

Comment XI. Page 37 under Temporal Matching of Toxicological Endpoint and Exposure Period, DAS commented that there was mismatch between the NOELs and exposure durations, and suggested there was a failure of communication between MT and WHS Branches.

<u>Response</u>: The mismatch characterize by DAS is due to the lack of toxicity studies with protocols which match the exposure duration of concern. This disparity is common in risk assessment and the weight of evidence is necessary to determine the most reasonable match. The potential overestimation and underestimation of risks were discussed in the Risk Appraisal section of the RCD.

In the draft RCD, a two-week amortized NOEL (40 mg/kg/day for 100 ppm at 6 hours/day, 5 days/week; Eisenbrandt *et al*., 1985) was used to address any exposure of 1 to 13 weeks. The specific scenario was the fumigator and tent crew: 3.67- 4 days/week from 1 week to < 1 year based on mean exposure value. DAS argued that the 2-week NOEL should not be amortized since human exposures were also 5 days per week. This is a reasonable argument if the label specifically limited the exposure to 5 days per week, or to one or two week intervals. In practice, workers are more likely to be exposed for several consecutive weeks during the year. Amortization is a means to reflect a lower potential NOEL due to <u>repeated</u> weekly exposures. While it may overestimate the risk associated with one or two week's exposure, it actually underestimates the risk for repeated weekly exposures, up to 13 weeks. For 13 weeks of exposure, the MOE was calculated using a subchronic NOEL of 12 mg/kg/day (3.5-fold lower than the 2-week NOEL). Therefore, there is no change to the 1-2 week NOEL.

Comment XII. Page 39 under Uncertainty, DAS considered the calculated dosages for acute and chronic NOEL to be underestimation.

Response: See responses to **Comments IV** and **IX**.

Comment XIII. Page 42 under Calculation of Margins of Exposure (MOE), DAS calculated MOEs all satisfy the minimum regulatory target of 100.

Response: In the August draft RCD, the recommended benchmark for MOE for bystanders is 1000, not 100, because of a 10-fold database uncertainty for the lack of a developmental neurotoxicity study. The U.S. EPA applied this factor in the evaluation of ProFume® registration and the registrant had concurred. In the previous RCD, the benchmark for workers and residents was 100. At that time, the developmental neurotoxicity study was not required by the U.S. EPA.

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Mary-Ann Warmerdam
Director

Department of Pesticide Regulation

M E M O R A N D U M

Arnold Schwarzenegger
Governor

TO: Joseph P. Frank, DSc., Senior Toxicologist
Worker Health and Safety Branch
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FROM: Roger C. Cochran, PhD, D.A.B.T., Staff Toxicologist (Specialist)
Worker Health and Safety Branch *(original signed by Roger Cochran)*
(916) 324-3516

DATE: November 4, 2004

SUBJECT: REVIEW OF DOW AGROSCIENCES LLC RISK CHARACTERIZATION DOCUMENT FOR SULFURYL FLUORIDE

Dow AgroSciences LLC (DAS) submitted a response to the Risk Characterization Document for sulfuryl fluoride in the form of a risk characterization using their own estimation of exposure (Registration Tracking ID No. SBRA-209121E). The most recent document is another repetition of the comments that were submitted by DAS on July 9, 2004. Those comments were fully responded to by Worker Health and Safety on July 27, 2004 (DiPaolo, 2004).

Reference:

DiPaolo, D., 2004. Response to comments from Dow Agrosciences LLC on draft sulfuryl fluoride risk characterization document. July 27, 2004. Memorandum from D. DiPaolo to J.P. Frank. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

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October 15, 2004

CLIENT/MATTER NUMBER
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VIA FACSIMILE

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Re: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S SULFURYL FLUORIDE RISK CHARACTERIZATION AND EXPOSURE ASSESSMENT DOCUMENTS

Mr. Segawa:

Thank you for this opportunity to review and comment on the Draft Sulfuryl Fluoride Risk Characterization Document. This firm represents Xtermite, Inc., a company that long-ago recognized the hazards of this acute toxic pesticide often used to control termites, and developed an alternative technology to control termites. As such, we have a unique understanding of these risk issues and the use of this pesticide in the termite control industry.

This draft risk characterization document is among the most comprehensive to date. The data contained in this report should serve as the foundation for regulatory action beyond just listing sulfuryl fluoride as a toxic air contaminant dangerous to bystanders, who typically are everyday people and their children living next door to a home tented for termite fumigation with this acute toxic chemical. Science has shown that at high exposure levels this toxic gas can cause death from respiratory failure. Other symptoms of its poisoning as it attacks the central nervous system can include depression, slowed gait, slurred speech, nausea, vomiting, stomach pain, drunkenness, itching, numbness, twitching and seizures. However, as requested, we will limit our comments to this document's accuracy in assessing risk to bystanders.

Overall, we find this document to be well articulated and comprehensive. However, there are areas of improvement that should be incorporated either in the final version or future reports to more accurately reflect real life circumstances in the application of sulfuryl fluoride during termite control.

The California Air Resources Board ("Air Board") identified several areas for improvement some of which the Department of Pesticide Registration ("DPR") incorporated in the report and some that need further revision. (*See* Draft Report, at Appendix E).

First, we agree with the Air Board that the report's assumption that 5 ppm is the bystander exposure near non-food commodity fumigation is not a health-protective assumption. As stated in the Air Board's comments, the 5 ppm level is the 8-hour permissible exposure level. A bystanders acute (1-2 hour) exposure level could be much higher, especially if California approves sulfuryl fluoride for food use as EPA has done. We would also go a step further than the Air Board's recommendation that DPR collect actual monitoring data at these facilities and recommend that DPR recalculate its figures with an additional safety factor to account for this uncertainty.

Second, we agree with the Air Board that due to the upward trend in pesticide use, DPR should use the most updated figures. We recognize that this draft report contains the updated 2002 use data. However, should the comment period uncover issues that delay the final report long enough, we respectfully request that the 2003 use data figures be used when they become available.

Third, the Air Board sought a clearer description of the location of the air monitors around a test site due to the concern that those monitors may not have been placed in a location necessary to measured the maximum downwind concentrations that a real life bystander would experience. In response, DPR confirms that the monitoring locations are noted in the report. We respectfully requests DPR confirm not only the location of the air monitors, but also the methodology used to determine the location of the maximum downwind concentration. This is critical information because in future regulatory actions, it may become necessary that applicators use monitors to assess wind direction and the scope of this toxic plume and deliver appropriate warning to bystanders in its path.

In addition to the Air Board, the Office of Environmental Health and Hazard Assessment ("OEHHA") reviewed and commented on this draft report. (*See* Draft Report, at Appendix F). Again, DPR incorporated some of those comments. We believe further revisions are necessary for a more accurate risk assessment.

First, we strongly agree with OEHHA's assessment that an additional ten-fold uncertainty factor is necessary to account for the current lack of a developmental neurotoxicity study and potential increase sensitivity of infants and children to sulfuryl fluoride exposures. Even if DPR concludes that infants and children are not more sensitive, the lack of a developmental neurotoxicity study alone was sufficient for USEPA to apply a ten-fold uncertainty factor. We are pleased DPR agreed with OEHHA's recommendation on applying an additional ten-fold uncertainty factor.

Second, we also believe it is appropriate to apply additional uncertainty factors for other sensitive populations, including the elderly and those with chronic breathing problems, such as common asthma. DPR asserts there is a lack of data and methodology for observing this, however, the very purpose of a risk assessment is to assign risk based on current knowledge and knowledge gaps making health-protective assumptions along the way.

Third, we agree with OEHHA's recommendation that DPR evaluate chronic and subchronic exposures to bystanders using the assumption that a family could live adjacent to more than one home being fumigated over the course of a year. The Worker Health and Safety Branch, responding

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on behalf of DPR, believes that it is not likely an individual bystander would be exposed to sulfuryl fluoride more than once a year. Common practice in the termite control industry would support OEHHA's assumption. Termite infestation tends to spread from house to house in a neighborhood either because subterranean termites infest and travel along wooden fences lines shared by neighboring properties or because winged termites easily travel the distances between houses. Often, before a homeowner is aware of a termite infestation problem in his home, it has already spread to neighboring households. Therefore, it is quite common for a series of households to require termite treatment in a single year. Not only is there a class of bystanders who are exposed at more than the study's assumed rate of once a year, there is also a class of hybrid bystander-residents who are exposed once from their neighbor's treatment and a second time from treatment in their own home. Worse yet, what if these household are occupied by infants, children, the elderly, or people with asthma? The compounding risk factors that can easily occur in real life application of sulfuryl fluoride need to be taken into account in this study. As such, we believe an appropriate uncertainty factor should be included for these compounding factors.

The regulatory history noted in the report demonstrates a clear trend toward increasing restrictions on sulfuryl fluoride as scientists discover more and more about its toxic effects. In 1959, sulfuryl fluoride was first registered. By 1985 when it was re-registered, scientific understanding of the chemical had advanced forcing EPA to order residue studies of the sulfuryl fluoride left behind in household food after a termite treatment. This led to a label warning that food and medicine should be removed or sealed when the product is used. In addition, EPA required all applicators to begin wearing respiratory protection devices. By 1993, additional scientific understanding of the dangers of this acute toxic chemical led EPA to issue a Reregistration Eligibility Document that concluded the 5 ppm level of indoor air concentrations allowed for residents to return to their homes no longer provided a sufficient margin of exposure. It recommended the reentry level be lowered to 2 ppm for adults and 1 ppm for children. Full blown self-contained breathing apparatus for applicators and new warning labels were also recommended. Nevertheless, the reentry level remains at 5 ppm and self-contained breathing apparatus are not yet required.

Add to the regulatory history this report's conclusions that sulfuryl fluoride may need to be listed as a toxic air contaminant in California, and the trend is clear that sulfuryl fluoride is fast becoming an acute toxic chemical that is no longer consistent with modern standards for protecting human health. Nevertheless, it is important that this conclusion be based on sound science. As currently drafted, this report takes another step in that direction. We believe the report should be modified further to take additional steps toward this seemingly inevitable conclusion.

Sincerely,

Jeffrey W. Forrest

Jeffrey W. Forrest
Attorney

cc: Anna Folkins

MEMORANDUM

TO: Gary Patterson, Ph.D.
Supervising Toxicologist
Medical Toxicology Branch

VIA: Keith Pfeifer, Ph.D., D.A.B.T. *[original signed by Keith Pfeifer]*
Senior Toxicologist
Medical Toxicology Branch

FROM: Lori O. Lim, Ph.D., D.A.B.T. *[original signed by Lori Lim]*
Staff Toxicologist
(916) 324-3515

DATE: May 10, 2005

SUBJECT: RESPONSES TO COMMENTS FROM JEFFERY W. FORREST ON DRAFT SULFURYL FLUORIDE RISK CHARACTERIZATION DOCUMENT FOR AB 1807 THE AIR TOXIC CONTAMINANT ACT

This memorandum addresses the comment on the toxicology and risk characterization submitted by Mr. Jeffrey W. Forrest at Foley and Lardner LLP, Attorneys at Law on behalf of Xtermite, Inc. (October 15, 2004) on the draft Risk Characterization Document (RCD; August 26, 2004) posted as part of the AB 1807, The Air Toxic Contaminant Act, public view process. The comments were primarily based on the reviews by the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA).

Comment I, Page 2, based on OEHHA review: The 10-x additional uncertainty factor is needed to address the lack of a developmental neurotoxicity study and increased sensitivity of infants, children, and other groups including elderly and those with chronic breathing problems, such as asthma.

Response: DPR agrees with the application of the 10x uncertainty factor for the lack of a developmental neurotoxicity study. DPR used the U.S. EPA approach to determine that there was no evidence of increased sensitivities of infants and children to the prenatal and post-natal toxicity (except for the developmental neurotoxicity) of sulfuryl fluoride. DPR has already incorporated a 10-fold factor to address intraspecies variation in response, which may be due to age and health status differences in the population.

TO: Joseph P. Frank, DSc.
Senior Toxicologist
Worker Health & Safety Branch
(916) 324-3517

FROM: Roger Cochran, PhD, D.A.B.T. , Staff Toxicologist (Specialist)
Worker Health & Safety Branch *(original signed by R. Cochran)*
(916) 324-3516

DATE: May 23, 2005

SUBJECT: Response to Foley & Lardner LLP: Comments on the Department of Pesticide Regulation's sulfuryl fluoride risk characterization and exposure assessment documents.

I apologize for not responding promptly to this letter, dated October 15, 2004, commenting on the exposure assessment for sulfuryl fluoride. The only comment necessitating a response from WH&S was: *"Third, we agree with OEHHA's recommendation that DPR evaluate chronic and subchronic exposures to bystanders using the assumption that a family could live adjacent to more than one home being fumigated over the course of a year. The Worker Health and Safety Branch, responding on behalf of DPR, believes that it is not likely an individual bystander would be exposed to sulfuryl fluoride more than once a year. Common practice in the termite control industry would support OEHHA's assumption. Termite infestation tends to spread from house to house in a neighbor hood either because subterranean termites infest and travel along wooden fence lines shared by neighboring properties or because winged termites easily travel the distances between houses. Often, before a homeowner is aware of a termite infestation problem in his home, it has already spread to neighboring households. Therefore, it is quite common for a series of households to require termite treatment in a single year."*

During the preparation of the exposure assessment for sulfuryl fluoride we were unaware of any information indicating that multiple adjacent homes are treated for termites or other pests by fumigation in a sequential manner during the course of a year. If the reviewer either has or is aware of such information, we should evaluate the work and incorporate any relevant data into the exposure assessment. I should point out that it was stated on page 45 of the Exposure Assessment, "Theoretically, it is possible for the four homes on each of the sides of the fumigated structure to also be fumigated in the same year. However, there are a number of factors (including economic considerations) that make more home fumigations in the same area unlikely." Unfortunately, we did not expand on this statement in the Exposure Appraisal section.

As noted by the reviewer, termite infestations can spread to homes without the residents' knowledge. However, we believe that they are unaware of such infestations without a home inspection. While we are not relying on empirical data, we do not consider it likely that homeowners commonly pay for a termite inspection of their homes when they become aware of their neighbor's home treatment. Furthermore, we believe that the type of termite treatment selected rests in part upon the type and degree of infestation. Not all infestations require fumigation. We also note that there are many effective treatments for termites that are less expensive and less invasive for the homeowner than fumigation. When all of these factors are taken into consideration, we feel that it is unlikely that several fumigations leading to 'seasonal exposures' will occur in neighboring homes in the course of a year.